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STUDIES ON THE CIRCULATION IN MAN

X. THE BLOOD-FLOW IN THE HANDS IN DISEASES OF THE HEART *

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CLEVELAND, O.

GENERAL REMARKS

It has been mentioned in the introduction to the last paper[1] that when proper precautions are taken there is a very fair degree of constancy in the results obtained in successive observations on different days on one and the same patient, provided gross changes in his clinical condition are excluded. Accordingly, a marked change in the flow not accounted for by changes in the external conditions, especially in the external temperature, always suggests some decided alteration in the clinical state of the patient. On the other hand, in certain cases, information may be obtained as to the state of the patient; for example, in regard to the lability of his vasomotor mechanism or the power of adaptation of his heart, by purposely changing the external conditions or by taking advantage of changes that have spontaneously occurred, in order to determine their effect on the flow in the hands or feet.

In comparing the flows in the whole series of cases investigated with those in normal persons, one is struck by the fact that while the flow in persons suffering from well characterized pathological changes (compensated valvular lesions, for example) may be of the normal magnitude, having regard to the age of the patient, the room temperature, etc., in a much larger number of cases it is below the normal, often greatly below it. Sometimes there is good evidence that this diminution in the hand or foot flow is the expression of an increased excitation of the vasoconstrictor mechanism as a whole or at least of the portion of it which presides over the cutaneous vessels not necessarily related to any material diminution in the driving power or the output of the heart. In other cases there is good evidence that the diminished flow in the hand (or foot) is in the main the expression of diminished functional capacity on the part of the heart, associated either with engorgement of the veins

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* From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

[1] Paper IX of this series.

and the right side of the heart or with diminution in the filling of the arteries without increased venous pressure. In still other cases evidence may be obtained of a diminished flow in one or both hands or feet, which is solely or mainly a local condition. A local increase in the flow may accompany such conditions as inflammation or vasomotor paralysis.

The question whether the flow in the hands or feet gives any indication of the functional capacity of the heart would be best discussed on the basis of an experimental comparison of the heart output, as determined gasometrically, with the hand flow in normal and pathological cases. Even in the absence of such a comparison, however, it would appear, that where the hand (or foot) flow is not less than normal it is only in exceptional conditions (local vasomotor paralysis of hands and feet?) that any gross error will be made in assuming that the heart is discharging an amount of blood not inferior to the normal. When, however, the flow in the extremities is permanently and decidedly less than normal, several points have to be considered. In many of these cases in which the normal ratio of the hand flow to the foot flow is preserved[2] in spite of the diminution in the flow and in which no anemia is present, there is often good evidence that the lessened driving power of the heart is primarily responsible for the diminished flow. On the other hand, in the anemias[3] the diminution of the flow in the hand and in the skin generally seems to be a compensating mechanism which permits an even increased quantity of blood to be sent by the heart through the lungs.

A marked disturbance of the normal ratio between the hand and foot flow, of course, gives no information as to the functional capacity of the heart, but indicates in the absence of local anatomical changes which might account for the difference (arteritis, paresis, etc.), a change in vasomotor excitability. Usually, this is manifested in a vasoconstriction of the feet, and a foot flow smaller than the normal in comparison to the hand flow. Since the feet are normally but little exposed in comparison with the hands, local vasoconstriction connected with the technic of the measurements is more likely to occur in the feet than in the hands. In various pathological conditions, for instance, fever,[4] where the vasoconstrictor mechanism of the skin is abnormally excitable the tendency of vasoconstriction in the feet on exposure is intensified. For this reason, as well as on account of the inferior flow per unit of volume in the feet, measurements of the hand flow are always to be preferred to measurements of the foot flow when the object is to obtain general information concerning the circulation and not to study local circulatory conditions. A disturbance of the normal ratio between the hand and foot flow, due not to vasomotor, but to anatomical causes (arteritis obliterans, for example), would be revealed by the fact that the ratio remains permanently abnormal even when the external conditions, the room temperature especially, are changed so as to abolish vasomotor differences of the lower and the upper extremities, or when this is done by the administration of vasodilator drugs.

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[2] See Paper VII of this series, Jour. Exper. Med., 1913, xviii, No. 1.

[3] Paper VI of this series, Jour. Exper. Med., 1913, xviii, No. 2.

[4] See Paper VIII of this series, Jour. of Exper. Med., 1913, xviii, No. 4.

A few words are necessary in regard to the classification of the cases dealt with in this paper. Some overlapping between the groups is unavoidable and the attempt has been made to assign each case presenting a complication of lesions to the group in which the factor seemingly predominant in the clinical picture would place it. For example, in the group of myocardial affections, cases are necessarily included in which there were definite and demonstrable valvular lesions. Thus certain cases with mitral stenosis (and insufficiency) are placed in the myocardial group because there is evidence that auricular fibrillation was also present, and that probably this condition with the consequent marked disturbance of the action of the ventricle was at the time of the investigation a more important factor in the clinical situation than the valvular lesion, or at least a factor which differentiated the case from one with the valvular lesion alone, and gave to it an added gravity. Among the few cases classed as arteriosclerosis, a group which might, of course, have been greatly swollen at the expense of the other groups had attention been paid solely to this condition, is one[5] which might also have gone with the valvular lesions. It is included with the cases of arteriosclerosis simply because that condition was extremely marked in the accessible arteries.

I. CONDITIONS IN WHICH SIGNS OF INVOLVEMENT OF THE MYOCARDIUM PREDOMINATED

There is probably no pathological condition of the heart in which such small hand flows are encountered as in this group. While the myocardium is acting well, grave valvular defects may, as is well known, be overcome, and the output remain for long periods quite at the normal level. The results of the blood-flow measurements in many cases of valvular lesions with good compensation are perfectly normal. With a heart whose myocardium is seriously crippled, even when the valves are anatomically and probably functionally intact, the hand flow may sink to astonishingly small figures. Nor is this difficult to understand. A pump with somewhat leaky valves may still deliver a good stream when the strokes are strong and regular. No matter how tight the valves are the output will be small if the stroke is feeble, uncertain and irregular.

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[5] Fred. S., Paper XI of this series.

Thus in Stephen F., a man 31 years old, the flow in the hands was only 0.2 gram per 100 c.c. of hand per minute with a room temperature of 23.5 C. increased to 0.5 gram in the right hand during immersion of the left in warm water, or not more than one-twentieth of the normal flow. The protocol of this case has already been published.[6]

The man, a contractor in a small way for brick and carpenter work, was examined in the dispensary and was admitted the same day to Lakeside Hospital where he died a few days later. He stated that between three and four years previous to admission he became ill after a heavy lift and had never been well since. All the signs of cardiac failure were present. To the left the cardiac dulness extended almost to the anterior axillary line. There was marked arhythmia with numerous premature contractions. For some time past he had been aware of the irregular action of his heart and stated that it sometimes stopped for a beat. The pulse-rate was only 60 (counted at the apex beat with the stethoscope). The neck veins were much engorged in the supine position. There was edema of the feet and ankles. The hands and feet were habitually cold although the weather was mild. The whole surface was pale and cool. There was no indication of valvular lesions. No murmurs were detected during the time the patient lived. The lungs were clear. The clinical diagnosis was myocarditis without valvular lesion. The immediate cause of death was pontine hemorrhage. At autopsy the findings were fibrous myocarditis with relative insufficiency but no valvular lesion, pericarditis, perihepatitis and atrophic cirrhosis of the liver, and acute pulmonary edema.

In Mrs. A., a woman aged 72, who came to the dispensary complaining of palpitation of the heart and irregular pulse, the blood-flow in the left hand came out 0.78 gram per 100 c.c. per minute, and in the right 0.45 gram, with room temperature 22.5 C. It must be taken into account that the hands in this case, being the typical hands of old age, consisted largely of bone, which has a small blood-flow.

The irregularity of the heart has been noticed for the past six years. The heart sounds were clear and no murmurs could be detected, but there was marked arhythmia. The pulse rate was 92 in sitting position. There was no edema, no cough. There was a history of rheumatism at 50 years of age, and again the winter before admission. The hands were very thin and rather cool, although she wore gloves and said they were as warm as usual. A diagnosis of senile heart with chronic myocarditis, arhythmia and arteriosclerosis was made. She continued to come periodically to the dispensary for over four months, still complaining of palpitation although the pulse became more regular.

The difference in the flow in the two hands (it must of course be noted that the accuracy of the measurements is less with these small flows than with normal flows) suggests that the smallness of the flow may be partly due to local vasoconstriction, which is often temporarily unequal for the two hands, and not altogether to the small output of the heart. The question may indeed be raised whether as in the anemias[7] a peripheral constriction may not occur in these cases in the interest of an increased flow through the lungs (and through the brain and other vital organs). In some ways the question is merely an academic one, since it is well known that in marked anemia the heart muscle may be impaired. It is clear that the percentage content and the total absolute amount of hemoglobin in the blood being normal, there may still be oxygen deficiency if the weakened heart is unable to propel the normal amount of blood from the left ventricle through the systemic vessels to the right side of the heart. On the supposition that the right ventricle could deal with a larger quantity of blood than is actually brought to it, a diminution in the average circulation time of the blood through the systemic path brought about by vasoconstriction confined to or predominating in the periphery might increase the minute volume of the heart. In this case the small hand flow, where the myocardium is seriously damaged, would be due to two things: First, diminished driving power of the heart; and second, constriction of the vessels of the peripheral parts in excess of that which would correspond to the diminished filling of the vessels due to the deficient action of the heart alone. Although the output in such cases as Stephen F. is diminished, it is not conceivable that it is diminished in the same proportion as the hand flow.

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[6] Cleveland Med. Jour., 1911, x, 385.

[7] Jour. Exper. Med., 1913, xviii, No. 2.

Jacob W., a house carpenter aged 59, height 5 feet, 1 inch, weight 173 pounds, was admitted at the dispensary April 4, 1911, suffering from myocarditis with anginal attacks. Six months previously while going to church he was suddenly seized with substernal pain, with great dyspnea. He had to sit down and could not speak. Since that time he has had a spell every morning, lasting two to five minutes and it is getting worse. If the pain is severe the left hand and forearm get dead. Since yesterday he has had palpitation. His general health was good until six months ago. He had rheumatism eighteen years ago. He used to drink beer and whisky moderately and to smoke moderately. He denies lues. Physical examination, cyanosis, some icterus; emphysema; heart generally enlarged; no murmurs. The heart sounds are weak; blood-pressure high; some sclerosis of the arteries. Urine negative.

He came periodically to the dispensary after this. April 24, 1911, his systolic blood-pressure was 190, diastolic 110. April 27, 1911, he had five attacks during the night. May 1, 1911, he had a mild attack while being examined in the dispensary. The pain was felt right beneath the sternum and radiated down the inner side of the left arm and up the neck to the chin. The pulse becomes somewhat smaller during the attack but the rate does not change. The heart is enlarged 4 cm. to the left but not to the right. He is still stout. He is being treated with potassium iodid and sodium nitrite. The blood flow in the hands was examined May 1, 1911. Mouth temperature 37.1 C. Pulse (sitting) 100, and rather small. Hands in bath at 2:44 p. m., in calorimeters at 2:55.* At 3:10 p. m. left hand put into water at 42.9 C. (Table 1.)

Cooling of calorimeters, R., 0.11 degrees in fourteen and one-half minutes; Left 0.14 degrees in twenty-one and one-half minutes. Volume of right hand, 508 c.c., of left hand 486 c.c. The hands were fat.

The flow in the right hand works out at 2.46 grams per 100 c.c. per minute, and in the left hand at 1.96 grams. When the left hand was immersed in warm water the flow in the right rose to 3.86 grams, a fair reflex vasodilatation. Subsequent immersion of the left hand in cold water caused little change in the flow in the right.

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* Three thousand and fifteen c.c. of water were put into each calorimeter. In the protocols, unless otherwise mentioned, this was the quantity always used for the hand calorimeters.

TABLE 1.—Calorimetric Measurements in Case of Jacob W.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
2:54	29.83	29.91	24.1	3:14	30.12	
2:56	29.81	29.86	.....	3:15	30.14	
2:57	29.82	29.86	.....	3:16	30.18	
2:58	29.84	29.87	.....	3:17	30.20	Room 25.0 C.
2:59	29.87	29.88	24.9	3:18	30.23	
3:00	29.87	29.89	.....	3:19	30.26	
3:01	29.88	29.91	.....	3:20	30.29	At 3:20 left hand put in water at 11.5 C.
3:02	29.89	29.92	.....	3:21	30.32	Room 25.1 C.
3:03	29.89	29.92	.....	3:22	30.34	
3:04	29.91	29.93	25.0	3:23	30.36	
3:05	29.92	29.94	.....	3:24	30.39	
3:06	29.93	29.94	.....	3:25	30.41	
3:07	29.95	29.95	.....	3:26	30.44	
3:08	29.98	29.97	.....	3:27	30.47	Left hand dried and wrapped.
3:09	29.99	29.98	.....	3:28	30.49	Room 25.1 C.
3:10	30.02	30.00	.....	3:29	30.51	
3:11	30.03	.....	.....	3:30	30.54	Hand out of calorimeter at 3:30.
3:12	30.05	.....	.....	3:31½	.....	Temp. of L. is now 29.86 C.
3:13	30.08	.....	25.2	3:44½	30.43	Temp. of L. is now 29.76 C.

In James M., a man 60 years old, with a very irregular pulse, enlarged heart and a history of edema of the feet and legs, the flow was 1.99 grams per 100 c.c. per minute in the right hand, and 1.35 grams in the left (for the last ten minutes in the calorimeters). Anemia was probably not an important factor in the small blood-flow, since the hemoglobin content of the blood was 80 per cent. three days before the examination. The calculated flows for the last twenty minutes in the calorimeters are 1.56 grams per 100 c.c. per minute and 1.06 grams for the right and left hands respectively, the ratio between the flows being precisely the same as for the last ten minutes (1.47:1).

James M., a laborer aged 60, was admitted to the City Hospital June 16, 1912. Three weeks before when in another hospital his feet and legs swelled and pitted on pressure. On admission to the City Hospital petechiae were present on both legs but there was no edema. The right side of the chest lags in inspiration and shows diminished resonance beginning at the sixth interspace in the axillary line, and also posteriorly. Fifteen months ago he had dyspneic attacks and the right pleural cavity was tapped. June 21, 1912, the right chest was aspirated but no fluid was obtained. The left border of heart dulness is outside the nipple line, the right border at the right margin of the sternum. The first sound is roughened. Pulse irregular, arhythmic, fair volume, sclerosis marked. The rectal temperature since his admission has varied from 100.4 to 98.2 F.

Examination of the blood-flow in the hands was made June 27, 1912, on which day he was discharged. Hands in bath at 1:34½ p. m.; in calorimeters at 1:43¾ p. m., and out of calorimeters at 2:15.

TABLE 2.—Calorimetric Measurements in Case of James M.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
1.43	31.02	31.12	.....	2.01	30.93	30.97	....
1.45	30.99	31.09	.....	2.02	30.93	30.965	....
1.46	30.98	31.08	22.9	2.03	30.93	30.955	23.0
1.47	30.98	31.07	.....	2.04	30.925	30.95	....
1.48	30.975	31.06	22.9	2.05	30.925	30.945	....
1.49	30.97	31.05	.....	2.06	30.93	30.94	23.1
1.50	30.965	31.04	23.0	2.07	30.925	30.935	....
1.51	30.96	31.03	.....	2.08	30.925	30.93	....
1.52	30.96	31.03	.....	2.09	30.93	30.93	23.1
1.53	30.955	31.025	23.1	2.10	30.925	30.93	....
1.54	30.95	31.02	.....	2.11	30.93	30.925	....
1.55	30.95	31.015	.....	2.12	30.925	30.925	....
1.56	30.94	31.005	23.1	2.13	30.93	30.925	23.0
1.57	30.94	31.00	.....	2.14	30.93	30.92	....
1.58	30.94	30.995	.....	2.15	30.925	30.915	....
1.59	30.935	30.99	.....	2.27	30.795	30.78	....
2.00	30.935	30.98	23.2				

Cooling of calorimeters in twelve minutes, R., 0.13 degrees; L., 0.135 degrees. Volume of right hand 368 c.c., of left hand 356 c.c. He is right handed,* wrists very thin, hands skinny. Pulse 87 (sitting). Very irregular. Rectal temperature 37.65 C. Water equivalent of calorimeters with contents, R., 3,389; L., 3,380. Blood-pressure, systolic 149 (palpation), 152 (stethoscope), 72 (sound gone). Another observation, systolic 144 (palpation).

A case diagnosed as auricular fibrillation (in N. P) is included under this heading, although there was a valvular lesion (mitral stenosis) present as well. The case did not come under my observation until the patient had improved considerably under treatment (digitalis), yet even then the flow in the hands was quite small for her age (1.97 grams per 100 c.c. per minute for the right hand, and 1.59 grams for the left for the last eleven minutes in the calorimeters). The small flow agreed with the persistent coldness of the hands and feet. It was not associated with anemia.

N. P., aged 27, was admitted for her present illness to the City Hospital March 12, 1913. (She was first admitted to the hospital April 4, 1910, suffering from rheumatism.) Heart: Apex beat visible in fifth interspace, one finger's breadth outside the nipple line. A presystolic thrill can be felt here. Left border two finger's breadth outside the nipple line; right border at the midsternal line, upper border at third rib. A rough presystolic murmur is heard over a small area at the apex. All over the precordia and transmitted to the axilla and back is heard a soft systolic murmur. The pulse shows marked arhythmia. Considerable edema. The urine, March 13, 1913, contained neither albumin nor casts. On May 12, 1913, there was some albumin but no casts. Under treatment (including digitalis) the pulse rate diminished. The arhythmia became less marked although it did not disappear, and the edema cleared up. Her appetite continues poor, but she sleeps well and is not troubled with dyspnea in any position. Her hands and feet are always cold. She says she is only really warm when surrounded by hot water bottles. Polygraph tracings from the jugular and radial taken on May 16, 1913, showed the ventricular form of venous pulse, "*a*" waves being absent from the jugular tracing. The rate of the heart in the semi-reclining position was 80 as counted at the apex with the stethoscope, and precisely the same at the wrist. The variation in the duration of successive beats is great. Twelve successive beats were measured in each of two portions of the tracing. In the first series the durations were 1.1, 0.8, 0.9, 0.8, 0.7, 0.65, 0.65, 0.5, 0.6, 0.9, 0.75, 0.9 second, the average being 0.77 second corresponding to 78 beats per minute. In the second series the durations were 0.85, 0.65, 0.75, 0.7, 0.7, 0.55, 0.75, 0.85, 0.9, 0.85, 0.95, 0.85 second, the average being 0.78 second corresponding to 77 beats per minute.

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* It can always be assumed that a patient was righthanded unless the contrary is stated in the protocols.

The blood-flow was examined May 12, 1913. Hands in bath at 2:43 p. m.; in calorimeters at 2:54½, and out of calorimeters at 3:16. Mouth temperature 36.3 C. (the thermometer was in five minutes and special care was taken).

TABLE 3.—Calorimetric Measurements in Case of N. P.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.54	31.56	31.41	.....	3.06	31.455	31.28	23.9
2.55	31.53	31.37	.....	3.07	31.45	31.27	....
2.56	31.51	31.36	24.2	3.08	31.45	31.27	....
2.57	31.50	31.355	.....	3.09	31.44	31.26	....
2.58	31.50	31.35	24.1	3.10	31.43	31.255	23.8
2.59	31.49	31.34	.....	3.11	31.43	31.25	....
3.00	31.49	31.33	.....	3.12	31.42	31.24	....
3.01	31.48	31.31	.....	3.13	31.42	31.235	....
3.02	31.46	31.30	.....	3.14	31.41	31.23	....
3.03	31.46	31.29	23.6	3.15	31.41	31.225	....
3.04	31.46	31.285	.....	3.16	31.405	31.215	....
3.05	31.455	31.28	23.9	3.35	31.19	30.995	....

Cooling of calorimeters in 19 minutes, R., 0.215 degrees; L., 0.22 degrees. Volume of right hand in calorimeter 298 c.c., of left hand 276 c.c. Pulse (sitting) 75 in one count, 66 in another, irregular and weak. It is not easy to count the pulse at the wrist because of the variability in the beat. Systolic blood-pressure in right arm 95. Difficult to determine the blood-pressure with the stethoscope.

A man 44 years old (Jacob S.), with mitral stenosis and insufficiency, an irregular heart, and weak and irregular pulse, from a study of whose case a diagnosis of auricular fibrillation was made, had a flow of only 1.97 grams per 100 c.c. per minute in the right hand, and 0.96 gram in the left, with room temperature 22.2 C. The disproportion in the flow in the two hands is associated with old hemiplegia of the left side. Immersion of the right hand in warm water caused a great percentile increase in the flow in the left hand (to 1.54 grams per 100 c.c. per minute for the first five minutes and 3.86 grams for the next four minutes), although the maximum was still absolutely a small flow. The fair crossed vasomotor reflex from the normal to the formerly paralyzed hand, which had largely recovered, contrasts with the absence of reflex in a case of old hemiplegia where there had been no recovery of the hand.[8]

Jacob S., a tailor aged 44, height 5 feet, 3½ inches, weight 140 pounds, first presented himself at the dispensary Oct. 27, 1910. Three years before he had rheumatism and had "heart trouble" at that time and also pneumonia. Eleven years ago when sitting in a chair he had a left-sided paralysis which came on him suddenly. He lost consciousness. He also had aphasia. He could understand what was said but could not speak. He recovered his speech in two months. The arm and leg recovered slowly. There was no disturbance of sensation at the time of the stroke, but two months later he had loss of sensation so that a pin could be stuck into his arm or leg without his knowing it. He burnt his left elbow severely without feeling it by leaning on a stove. The lines on the left side of the face are not so deep as on the right. He drags the left foot somewhat. The tongue is protruded in the median line. The reflexes are much increased in both upper and lower extremity. Babinski's sign can be obtained on the left side. Touch and pain are normally appreciated on the left side but heat cannot be distinguished over the left arm. The physical signs of chronic bronchitis and emphysema are present. Heart slightly enlarged both to right and left. Pulmonic second sound accentuated. The heart sounds are very irregular both in force and rhythm. Pulse rate 80.

Nov. 5, 1910, a marked presystolic murmur and thrill can be made out.

Dec. 10, 1910, he is very dyspneic and cannot sleep. Ears, fingers, tip of nose and lips are cyanotic. Positive venous pulse in the neck. The heart dulness extends two fingers outside the nipple line on the left side and two fingers outside the sternal margin on the right. There is a sharp first sound preceded by a faint presystolic murmur and followed by a systolic murmur. The pulse is small, irregular and of very poor volume and tension. The left radial pulse is smaller than the right. The liver is increased in size to percussion. He was received into the hospital to-day where he improved. Blood-pressure, systolic 162, diastolic 120. Blood: leukocytes, 10,500; hemoglobin, 90 per cent.

April 11, 1911, he returned to the dispensary in about the same condition as before he entered the hospital. Pulse rapid and irregular.

April 25, 1911, enlargement of the heart and arhythmia is still marked. Knee-jerk much exaggerated on the left side. When he gets out of breath he feels the left hand getting stiff. The difference in size of the two hands is not conspicuous. The great difference in the two arms is in the girth of the shoulders, the left shoulder being much smaller than the right. He cannot completely extend the left forearm on the elbow owing to contracture. Sometimes when he is grasping an object in his left hand the fingers remain closed around it involuntarily and he has to release the object with the other hand. He lost sexual power at the time of the stroke and has not regained it. He has been constipated since the stroke and has had to use cathartics constantly.

The blood-flow in the hands was measured April 25, 1911. Pulse (sitting) 104. Mouth temperature 36.25 C. Hands in bath at 2:31 p. m., in calorimeters at 2:42.

At 2:55 p. m. the right hand was put into water at 43.3 C.

Calorimeter R. was constantly stirred until 3:10 p. m. After this R. and L. were only stirred occasionally. Cooling of R. from 2:55 to 3:10½ is 0.18 degree (in fifteen one-half minutes.) Cooling of R. from 3:10½ to 3:27 (with little stirring) is 0.15 degree (in sixteen one-half minutes.) Cooling of L. from 3:10½ to 3:28 (with little stirring) is 0.16 degree (in seventeen one-half minutes.) Accordingly with little stirring L. cooled at the same rate as R. We can therefore assume that with constant stirring this would also be true and that the amount of cooling for L. during the observations is 0.18 degree in fifteen and one-half minutes. Volume of right hand 390 c.c., of left hand 378 c.c.

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[8] Heart, 1911, iii, 81.

TABLE 4.—Calorimetric Measurements in Case of Jacob S.

Time	Right	Left	Temp. Room C.	Time	Left	Notes
2:41	29.73	29.72	.....	2:58	29.60	
2:43	29.68	29.65	.....	2:59	29.60	Room 22.7 C.
2:44	29.68	29.65	22.0	3:00	29.60	
2:45	29.68	29.64	.....	3:01	29.59	
2:46	29.68	29.64	.....	3:02	29.61	
2:47	29.67	29.63	.....	3:03	29.62	
2:48	29.67	29.63	.....	3:04	29.63	
2:49	29.67	29.62	.....	3:05	29.64	At 3:05 right hand dried and wrapped.
2:50	29.68	29.63	.....	3:06	29.64	
2:51	29.68	29.62	.....	3:07	29.65	
2:52	29.68	29.61	22.4	3:08	29.65	
2:53	29.69	29.61	.....	3:09	29.67	
2:54	29.69	29.60	.....	3:10	29.68	At 3:10 hand out of calorimeter.
2:55	29.70	.....	.....			
2:56	.....	29.60	22.6	3:10½	.....	Temp. of R. is now 29.52 C.
2:57	.....	29.59	.....	3:27	.....	Temp. of R. is now 29.37 C.
				3:28	29.52	

In a third case diagnosed as one of auricular fibrillation (T. F. K.), a man 57 years old, the flow was 4.45 grams per 100 c.c. per minute for the right hand, over an eighteen-minute period, and 5.23 grams for the left hand (ratio of the flows in the two hands 1:1.17). For the last nine minutes of this period, the flows were 6.21 grams and 7.06 grams, respectively, for the right and left hands (ratio of the flows in the two hands 1:1.13). These are fair flows for the man's age, indicating that the heart in spite of the irregular action of the ventricle is maintaining a fair output. This corresponds entirely with the clinical condition at the time of the blood-flow examination. The edema had completely disappeared. There was no dyspnea. The appetite was good and the patient was no longer confined to his bed. Many of the pulse beats at the wrist were of good amplitude, although others were small (Fig. 1), while in the case of N. P. all of the beats were small.

T. F. K., a bricklayer, aged 57, height 5 feet, 9½ inches, weight 140 pounds, was admitted at the City Hospital May 1, 1913. He had typhoid about thirty years ago and rheumatism sixteen or eighteen years ago. His present illness began last November. His ankles became swollen and also his legs, nearly up to the hips, and he lost strength and weight rapidly. He noticed at the same time that his pulse was irregular. He had pain in the right side of the chest. The swelling in the legs had diminished somewhat before he entered the hospital, but on admission edema and cyanosis were still to be observed. His chest was barrel-shaped with broad costal angle and poor expansion. No râles or dulness over the lungs, but there was a friction rub over the anterior surface of the right lung. The cardiac impulse was diffuse, and extended considerably beyond the nipple line on the left side. Cardiac dulness enlarged to the left. The liver was somewhat enlarged and pulsation evident in the epigastrium. The veins in the neck were distended. A systolic murmur was heard over the apex. His maximum temperature (on May 9) was 103.6 F., minimum 97.4 on the same day. The maximum temperature on May 16 was 102; May 17, 102; May 19, 101.4 F. The pulse-rate on May 1 was 120; May 19, 92. The pulse-rates were usually above 90. The radial pulse is markedly irregular in amplitude and rhythm, and the irregularity is not affected when respiration is suspended. Polygraph tracings from the distended external jugular vein and the radial artery showed that the venous pulse was of the ventricular character (Fig. 1). Diagnosis, auricular fibrillation. The blood-flow in the hands was examined May 19, 1913, at which time the swelling had entirely disappeared from the lower extremities and the patient was allowed to sit up for a portion of the day. Hands in bath at 3:14 p. m.; in calorimeters at 3:26¾, and out of calorimeters at 3:47.

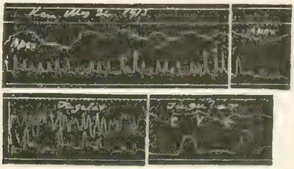

Fig. 1.—Upper part of tracing, simultaneous record of apex beat and radial pulse. The respiratory movements interfered with the apex trace except towards the end of expiration. At the right is a portion of the apex tracing which allows a sufficiently good comparison to show that some of the apex beats are only feebly represented on the radial trace. The lower portion of the figure gives simultaneous tracings from the external jugular and the radial. As in all tracings, time is marked in fifths of a second. (All tracings reduced to about one-half size of originals.)

TABLE 5.—Calorimetric Measurements in Case of T. F. K.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.26	31.59	31.48	.....	3.38	31.63	31.59	24.0
3.28	31.56	31.46	23.5	3.39	31.66	31.625	....
3.29	31.565	31.47	.....	3.40	31.695	31.665	23.95
3.30	31.57	31.475	.....	3.41	31.72	31.685	....
3.31	31.57	31.48	.....	3.42	31.74	31.73	....
3.32	31.57	31.485	.....	3.43	31.78	31.76	24.0
3.33	31.58	31.50	24.2	3.44	31.79	31.77	....
3.34	31.58	31.50	.....	3.45	31.82	31.82	24.1
3.35	31.59	31.525	.....	3.46	31.84	31.86	....
3.36	31.60	31.55	.....	3.47	31.88	31.90	....
3.37	31.62	31.56	.....	4.16	31.52	31.555	....

Cooling of calorimeters in 29 minutes, R., 0.26 degrees; L., 0.245 degrees. Volume of right hand in calorimeter 444 c.c., of left hand 458 c.c. He is left handed. Water equivalent of calorimeters with contents, R., 3,450; L., 3,461.

Rectal temperature 37.35 degrees. Blood-pressure in left brachial, maximum systolic (when the larger pulsations begin to be heard) 111, 58 (sound gone). Another observation, maximum systolic 114, 58 (sound gone).

In two cases in which acute symptoms diagnosed as due to myocarditis had been present, but which had markedly improved under treatment so that the patients were able to come without trouble to the dispensary, a fair hand flow was found. Both were men 59 years old. In one of these patients (J. S. W.) who had been in the hospital two years before and had been near death, the flow was 6.82 grams per 100 c.c. per minute in the right hand and 6.58 grams in the left, with room temperature at 21.9 C. Simultaneous tracings from the jugular bulb, the radial artery and the apex showed that the "*c*" wave was notably large; the *a* wave was also well marked. All the ventricular beats were recognizable on the radial trace.

J. S. W., a fireman, colored, height 5 feet, 10 inches, weight 160 pounds, born in 1851, was first admitted to the dispensary Feb. 21, 1905, complaining of pain in chest and cough. The heart sounds were faint but clear. No murmurs. Heart dulness enlarged to the left well beyond the mammary line. The pulse was irregular. A diagnosis of myocarditis was made. April 13, 1908, he was again admitted to the dispensary. Heart enlarged to the left two fingers breadth beyond the mammary line. Pulse rapid and irregular. Some albumin in the urine. Nov. 4, 1908, he was admitted to Lakeside Hospital and again on Feb. 20, 1909. He had attacks of syncope with fluttering in the chest and came near death. The pulse-rate was 120, systolic blood-pressure 160. Pulse regular and all the beats reached the wrist. Under treatment the pulse rate diminished and as it slowed the arhythmia returned (premature contractions). March 19, 1909, the rate was 68, systolic blood-pressure 160. Tracings from the bulbus venosus showed well marked *a*, *c* and *v* waves of which the *c* wave was very large. Presystolic, systolic and diastolic pulsations were visible over the jugular bulb. He was discharged from the hospital May 5, 1909, improved. Oct. 5, 1909, he reported at the dispensary that he had gained 20 pounds since leaving the hospital. Oct. 4, 1910, he was feeling better, but had occasional smothering sensations. There was now no arhythmia and no albumin in the urine.

TABLE 6.—CALORIMETRIC MEASUREMENTS IN CASE OF J. S. W.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.10	29.40	29.29	.....	3.22	29.96	29.86	....
3.14	29.47	29.38	.....	3.23	30.00	29.91	....
3.15	29.53	29.43	.....	3.24	30.08	29.97	....
3.16	29.59	29.50	.....	3.26	30.20	30.10	....
3.17	29.66	29.55	.....	3.27	30.23	30.12	....
3.18	29.73	29.61	.....	3.34	30.16	30.06	....
3.19	29.78	29.67	.....	3.39	30.09	30.00	....
3.20	29.83	29.71	.....	3.51	29.96	29.88	....
3.21	29.89	29.80	.....				

The flow in the hands was measured Jan. 10, 1911. He feels much improved. Systolic pressure still very high; when last taken 210. Hands in bath at 3:00 p. m.; in calorimeters at 3:11½, and out of calorimeters at 3:27; 3,050 c.c. of water in each calorimeter. Room temperature 21.7 C. (Table 6.)

Volume of right hand 570 c.c., of left hand 570 c.c. His hands are very large. Pulse 60 (sitting). Mouth temperature 36.5 C. Rectal temperature 37.6 C. Room temperature at end of observations 22.2 C.

Since this time he has continued to report at the dispensary and has been more than once in the hospital with the signs of cardiac breakdown. On Dec. 7, 1912, "the left border of the cardiac dulness is at the anterior axillary line, and the right one finger's breadth beyond the right sternal border, heart thumping and somewhat irregular. Feb. 11, 1913, spitting blood and short of breath. Right border of cardiac dulness two fingers breadth to right of sternal margin. Sounds distant and irregular. No murmurs. Râles throughout both lungs." In June, 1913, eight years from the beginning of his illness, he was still coming to the dispensary and had periods of temporary improvement.

The other patient (Peter B.) was twice examined. At the first examination he had a flow of 6.44 grams per 100 c.c. of hand per minute in the right hand and 5.99 grams in the left, with room temperature 24.5 C. This is by no means a large flow for the temperature, and while fair reflex vasodilatation was obtained by the application of warmth to the contralateral hand, cold did not cause vasoconstriction sufficient to reduce the flow to the initial amount. This agrees well with the fact that arteriosclerosis was distinct, for reflex vasoconstriction is not well obtained in this condition. Almost a month later his hand flow was again measured. He had meanwhile much improved. The flow was 9.95 grams per 100 c.c. per minute for the right and 7.46 grams for the left hand. However, the room temperature was relatively high (26.6 C.), and this probably accounted for a portion of the increase in the flow. The vasodilatation consequent on the high external temperature was considerable and permitted a small reflex vasoconstriction when the contralateral hand was immersed in cold water.

Peter B., a janitor, aged 59, height 5 feet, 2 inches, weight 126 pounds, was under observation at the dispensary with symptoms diagnosed as due to myocarditis. For many years he did heavy work in a gas works. Though his work is now light he has had to give it up for the present. He suffered greatly from rheumatism till about fifteen years ago, since which time he has not been troubled. His joints would swell and he could not walk. He is married and has seven children, all in good health. His present illness dates from somewhat less than two years ago, when he suddenly became unconscious while mowing the lawn. He remained unconscious for five minutes. Three months later he had another attack. He came to the dispensary a number of times, and the records state that he had a slow pulse (60 a minute). The intervals between attacks became gradually shorter, and they occurred about once in six weeks. He falls down and "goes stiff" (extensor spasm) and now he sometimes has two attacks in a week. He seems particularly liable to become unconscious in bed. When he arises after bending down he is blind for about two minutes. Pupil reactions to light and accommodation are normal. He has long suffered from chronic bronchitis. Since the present trouble began his feet are always cold. Previously they used to be very hot and perspired greatly. He does not feel that his hands are cold. Physical examination negative for lungs. Heart dulness two finger's breadth to left of nipple. Sounds clear, distant, the first a little shortened. No accentuation of aortic or pulmonary. Arteries somewhat thickened. Pulse slow, fair volume, well sustained, easily compressible; rate 62. Marked slowing when the vagi are compressed in the neck. There is a venous pulse in the neck.

The flow in the hands was first examined April 21, 1911. Pulse (sitting) 80. Mouth temperature 36.45 C. Room temperature 24.8 C. Hands in bath at 2:31½ p. m., in calorimeters at 2:42. At 2:53 left hand put into water at 42.9 C.

TABLE 7.—Calorimetric Measurements in Case of Peter B.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
2:40½	30.04	30.03	.....	3:00	30.57	
2:43	30.01	30.02	.....	3:01	30.60	
2:44	30.03	30.03	24.7	3:02	30.63	
2:45	30.06	30.06	.....	3:03	30.69	At 3:03 put left hand in water at 8 C.
2:46	30.09	30.09	.....	3:04	30.71	Room 24.3 C.
2:47	30.11	30.10	.....	3:05	30.77	
2:48	30.14	30.12	.....	3:06	30.79	
2:49	30.17	30.14	.....	3:07	30.81	
2:50	30.20	30.18	.....	3:08	30.83	
2:51	30.24	30.21	24.3	3:09	30.87	
2:52	30.28	30.23	.....	3:10	30.89	
2:53	30.30	30.25	.....	3:11	30.91	At 3:11 dried left hand and exposed it for inspection. Then wrapped it in warm cloth.
2:54	30.32	.....	.....	3:12	30.93	
2:55	30.36	.....	24.4	3:13	30.97	
2:56	30.40	.....	.....	3:14	31.00	Room 24.2 C.
2:57	30.44	.....	.....	3:15	31.04	Hand out of calorimeter at 3:15.
2:58	30.49	.....	24.2	3:30	30.89	At 3:30 temp. L. 29.95 C.
2:59	30.52	.....	.....			

Cooling of calorimeters, R., 0.15 degree in fifteen minutes; L., 0.30 degree in thirty-seven minutes. Volume of right hand 360 c.c., of left 320 c.c. Water equivalent of calorimeters with contents, R., 3,383; L., 3,351.

Second examination May 17, 1911. He is feeling much better than when last examined. He was being treated with potassium iodid and nitroglycerin. Although he has had slight attacks of dizziness and "feeling stupid," he has not fallen or "gone stiff." There is no arhythmia now, nor can any murmurs be detected. Pressure on the vagus in the neck readily inhibits the heart causing the pulse at the wrist to disappear for a beat or two. He feels dizzy during the compression, and he can be made unconscious at any time by pressing on the vagus.

Hands in bath at 2:33 p. m., in calorimeters at 2:43½; mouth temperature 36.5 C.; pulse (sitting) 84. At 2:55 p. m. left hand put into water at 8 C.

Cooling of calorimeters, R., 0.07 degree in ten minutes; L., 0.17 degree in twenty-nine minutes. Volume of right hand in calorimeter 410 c.c., of left hand 394 c.c. The marks were put higher up than usual as his hands were short. The lower mark was about the middle instead of the lower border of the styloid process of the ulna. He seemed gradually to improve and reported at his last visit to the dispensary, June 7, 1911, that he was better. Pulse 84. (See Table 8.)

II. VALVULAR LESIONS

The flow in these cases may be normal or much less than normal, depending on the degree of compensation. Since anemia may be associated with a valvular lesion, it may be a factor in diminishing the hand flow in the way already discussed in a previous paper.[3] Since, further, the degree of involvement of the myocardium will differ in different cases with one and the same valvular lesion, it is not to be expected that a relatively large flow should always be associated with one particular type of valvular defect and a small flow with another. Nevertheless, so far as can be judged from the series of cases examined, certain of the valve lesions are more apt to be associated with the normal flow than others or even with a flow somewhat above the normal. Mitral insufficiency, for instance, it would seem, is less likely to be associated with a diminished hand flow than aortic insufficiency. In the only case in which a diagnosis of pure aortic stenosis seemed justified, the hand flow was normal, and this agreed with the clinical condition of the patient, who indeed did not enter the hospital for his heart lesion, but for a surgical cause. To emphasize the fact, however, that the mere naming of the valvular lesion is no indication of the amount of the hand flow, we shall begin the description of this group of cases with one of mitral incompetence in which the flow was very markedly diminished.

TABLE 8.—Calorimetric Measurements in Case of Peter B. Second Test

Time	Right	Left	Room Temp. C.	Time	Right	Notes
2:43	30.29	30.18	.....	3:00	31.125	
2:45	30.35	30.22	26.4	3:01	31.16	
2:46	30.42	30.27	.....	3:02	31.195	
2:47	30.51	30.32	.....	3:03	31.23	
2:48	30.57	30.38	26.5	3:04	31.29	
2:49	30.63	30.425	.....	3:05	31.325	At 3:05 left hand put in water at 43 C.
2:50	30.68	30.455	.....	3:06	31.355	
2:51	30.73	30.50	.....	3:07	31.38	
2:52	30.79	30.535	.....	3:08	31.41	
2:53	30.835	30.57	.....	3:09	31.44	
2:54	30.88	30.60	.....	3:10	31.475	Room 26.7 C.
2:55	30.915	30.625	.....	3:11	31.505	
2:56	30.94	.....	.....	3:12	31.53	
2:57	30.99	.....	26.8	3:13	31.565	
2:58	31.035	.....	.....	3:14	31.59	Room 26.6 C. Hand out of calorimeter at 3:14.
2:59	31.08	.....	.....	3:24	31.52	At 3:24 temp. L. 30.455 C.

John T., contractor, aged 28, height 5 feet 6 inches, was admitted to the City Hospital March 31, 1912, with edema of the legs and hands and considerable cyanosis. A systolic murmur can be heard at the apex of the heart. The apex beat is visible and palpable with a heaving impulse in the sixth interspace in the nipple line. There is pulsation in the suprasternal notch. The cardiac dulness in the sixth left interspace is three fingers breadth outside the nipple line. The radial pulse is not easy to feel on account of the edema. It is small in volume and tension but has a regular rhythm. The urine contains albumin. He was treated with digitalis. April 9, 1912, the blood-flow in the hands was examined. Hands in bath at 2:21 p. m., in calorimeters at 2:31. He had some cough during the observations. Systolic blood-pressure 122. Pulse 70. At 2:47 p. m. left hand put into water at 42.7 C.

TABLE 9.—Calorimetric Measurements in Case of John T.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
2:30½	31.40	31.49	.....	2:48	31.385	
2:32	31.35	31.44	24.3	2:49	31.385	
2:33	31.35	31.44	.....	2:50	31.39	Room 24.3 C.
2:34	31.34	31.43	.....	2:51	31.39	
2:35	31.34	31.43	24.1	2:52	31.395	
2:36	31.335	31.425	.....	2:53	31.395	
2:37	31.335	31.425	.....	2:54	31.395	
2:38	31.34	31.43	.....	2:55	31.40	Hand out of calorimeter. Room 24.3 C.
2:39	31.345	31.435	.....	3:11	31.23	At 3:11 temp. L. 31.225 C.
2:40	31.35	31.435	.....			
2:41	31.35	31.435	24.3			
2:42	31.36	31.435	.....			
2:43	31.365	31.44	.....			
2:44	31.37	31.445	.....			
2:45	31.37	31.45	.....			
2:46	31.38	31.455	24.6			
2:47	31.38	31.455	.....			

Cooling of calorimeters, R., 0.17 degree in sixteen minutes; L., 0.23 degree in twenty-four minutes. Volume of right hand 450 c.c., of left hand 438 c.c. Water equivalent of calorimeters with contents, R., 3,455; L., 3,445. Rectal temperature 37.95 C.

April 24, 1912, he was discharged "improved."

In this case the flow was only 2.09 grams per 100 c.c. of hand per minute in the right hand, and 1.67 grams in the left, with room temperature 24.4 C., a flow very much too small for his age.

In a case of mitral stenosis, mitral and tricuspid insufficiency in a man 63 years old (James H.), the flow, measured on an exceedingly hot day with a room temperature of nearly 31 C., was 7.31 grams per 100 c.c. of hand per minute for the right hand and 6.41 grams for the left. Probably not more than one-third to one-half of the flow to be expected in a healthy young adult for that room temperature. Measurements made at such high room temperatures do not lend themselves readily to comparisons. The examination was made on this day purposely to observe the effect of maximal vasodilatation on the flow in this case, since at two previous examinations the hand flow seemed to be greatly diminished by persistent local vasoconstriction which the patient attributed to the low temperature of the wards. He said he had felt chilly all the time, but to-day he felt warm. The pulse showed arhythmia (Fig. 2), partly respiratory.

James H., a hatter, aged 63, admitted to the City Hospital May 2, 1913, suffering from chronic endocarditis with mitral stenosis and insufficiency and tricuspid insufficiency. No history of rheumatism. He complains of weakness and shortness of breath for the last three or four weeks. His feet swell at times. Ears, lips, nails and mucous membranes were markedly cyanotic on admission. There was slight edema of the legs with great varicosity of the leg veins. Marked engorgement and pulsation of the veins of the neck. Lungs revealed nothing special on physical examination. Heart enlarged. Left border of cardiac dulness at the anterior axillary line in the sixth interspace; right border 3 cm. to right of sternum. A presystolic thrill followed by impact and systolic thrill palpable over apex. Liver pulsatile and the lower edge palpable 8 cm. below the costal margin. Radial pulse markedly irregular and arhythmic with fair volume and tension, fairly well sustained. He was discharged May 17 improved. He went to work but became ill again and returned to the hospital May 23, 1913.

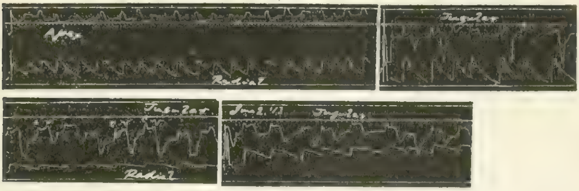

Fig. 2.—Tracings from James H.

TABLE 10.—Calorimetric Measurements in Case of James H.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.00	31.30	31.24	.....	2.17	31.07	30.98	23.3
2.02	31.25	31.17	23.1	2.18	31.055	30.97	....
2.03	31.23	31.16	.....	2.19	31.04	30.96	....
2.04	31.22	31.15	.....	2.20	31.03	30.955	23.4
2.05	31.20	31.13	23.3	2.21	31.02	30.95	....
2.06	31.19	31.12	.....	2.22	31.01	30.945	....
2.07	31.18	31.105	23.3	2.23	31.00	30.94	23.4
2.08	31.17	31.09	.....	2.24	30.995	30.93	....
2.09	31.15	31.08	23.2	2.25	30.995	30.925	....
2.10	31.13	31.06	.....	2.26	30.99	30.915	23.5
2.11	31.125	31.055	.....	2.27	30.98	30.90	....
2.12	31.11	31.05	23.2	2.28	30.975	30.895	....
2.13	31.10	31.04	.....	2.29	30.97	30.89	....
2.14	31.09	31.03	23.2	2.30	30.96	30.88	23.6
2.15	31.08	31.01	.....	3.21	30.395	30.34	....
2.16	31.07	30.99	.....				

The first examination of the hand flow was made on May 29, 1913. His hands were cold when he was brought into the room, having been exposed for some time near an open window. The day, however, was not especially cool. He was allowed to keep the hands wrapped up for twenty minutes in his gown before the observations were begun. Pulse 70 (sitting). The volume of the pulse seemed fair and was thought to indicate a much better flow than was actually shown by the examination, but the veins on the back of the hands, although prominent, filled but slowly when emptied of blood. Hands in bath at 1:50 p. m.; in calorimeters at 2:00½, and out of calorimeters at 2:30.

Cooling of calorimeters in fifty-one minutes, R., 0.565 degree; L., 0.54 degree. Volume of right hand 418 c.c., of left hand 396 c.c. The hands do not feel cold to the touch on coming out of the calorimeters. They are fairly red. The veins on the back of the hand and in the forearm are large, but fill with marked slowness on being emptied. Blood-pressure, left arm, systolic 136, 63 (sound gone). Another observation 134, 68. There was no sensible interval between the change in sound and its disappearance. A few of the larger beats were heard a little before the readings given as systolic pressure. The number of waves coming through increased as the pressure fell.

The flow in the hands in this examination works out at only 0.80 gram per 100 c.c. per minute for the right hand, and 0.64 gram for the left, for the last ten minutes of immersion in the calorimeters. If the whole period in the calorimeters is taken, the calculated flow is still less, as is always the case with a very small flow, the period required for the attainment of the steady state where the thermometers are changing uniformly being long.

A second examination on June 2, 1913, gave an even smaller calculated flow (0.40 gram per 100 c.c. per minute) for the last ten minutes in the calorimeters. The temperature readings followed precisely the same course as at the first examination. The question arises how such small flows can be reconciled with the fairly good volume of the arterial pulse at the wrist. The explanation is found partly in the fact that the venous return was hindered as indicated by the appearance of the veins. The increase in venous pressure while it did not hinder the conduction of the arterial pulse wave, apparently diminished the rate of translation of the blood. A second factor in the small flow was apparently a persistent local vasoconstriction in the hands. That this second factor was concerned is shown by the great improvement in the hand flow at the third examination, although the pulse-rate, far from being accelerated, was even slower than at the previous examinations.

Third examination June 16, 1913. He is feeling well, only weak. No dyspnea and no cough whatever. The day is very warm and the room temperature the highest in the whole series of observations. The veins on his hands and arms fill much more quickly after being emptied than on the two previous occasions. Amplitude of the pulse at the wrist is fair, but not strikingly greater than at the other examinations. Pulse 57 (sitting), with some irregularity but not so marked as before. Hands in bath at 4:06½ p. m.; in calorimeters at 4:15½, and out of calorimeters at 4:27.

Cooling of calorimeters in ten minutes, R., 0.045 degree; L., 0.04 degree. Volume of right hand in calorimeter 408 c.c., of left hand 392 c.c. Water equivalent of calorimeters with contents, R., 3,421; L., 3,409. Blood-pressure in left brachial, systolic 110, another observation 106, 80 (change in sound). Rectal temperature 37.6 C. (See Table 11.)

The general cutaneous vasodilatation at the third examination was evident and is doubtless related to the decidedly diminished systolic pressure. The hands shared in this general vasodilatation, and it is probable for this reason that the hand flow gives an index to the heart output. Since the hand flow with practically maximal vasodilatation is not half that of a young adult at this room temperature, the heart output is probably at most 50 per cent. of that of a healthy young adult. The three observations together show that in this man of 63 the range of the vasomotor adaptation of the hand blood-vessels is still considerable, a confirmation of his statement that the hot weather suited him.

TABLE 11.—Calorimetric Measurements in Third Examination of James H.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
4.15	31.45	31.50	.....	4.22	31.71	31.72	30.9
4.16	31.46	31.52	.....	4.23	31.765	31.76	....
4.17	31.49	31.54	.....	4.24	31.795	31.83	....
4.18	31.54	31.58	30.8	4.25	31.86	31.84	30.9
4.19	31.58	31.62	.....	4.26	31.89	31.87	....
4.20	31.62	31.655	30.9	4.27	31.925	31.90	....
4.21	31.67	31.69	.....	4.37	31.88	31.86	....

From the standpoint of the technic of the method it ought still to be mentioned that a local vasoconstriction so persistent as not to be overcome during the usual period of an examination (the disappearance of it being shown by a rather abrupt and henceforth steady rise of the thermometers) is rare in hospital cases, although in hands long exposed to cold it may be frequently met with. Where it exists the results cannot, of course, be used as average flows for the patient in question, although the intensity and persistence of the vasoconstriction may be of interest in relation to the patient's condition.

In a case of badly broken compensation in a boy (Joseph Z.), 16 years old, suffering from chronic endocarditis with aortic insufficiency and stenosis and mitral insufficiency, the flow in the right hand was 6.28 grams per 100 c.c. per minute, and in the left hand 4.79 grams. This is much too small for the age of the patient and the very high room temperature (28.1 C.). He was obviously in bad condition. Immersion of the left hand in cold water was followed by but a small diminution of the flow in the right, and immersion of the left hand in warm water by no increase at all, either because the dyspneic condition of the blood caused increased stimulation of the vasoconstrictors of the hand which the vasodilator effect of warmth to the contralateral hand could not overcome, or because the vasoconstrictor tone was already much diminished under the influence of the warm room, although, owing to the handicap of the heart, this was not shown in a large flow. Another possibility is that the dyspneic condition of the blood may have rendered the vasomotor centers less excitable to this form of afferent stimulation.

Joseph Z., boy aged 16, was admitted to the dispensary Nov. 11, 1910, suffering from aortic insufficiency and stenosis with attacks of acute pulmonary edema. He has had rheumatism for ten years. He was in the hospital three weeks for heart trouble which started four years ago. Has dyspnea and weakness. His heart is enlarged 16 cm. to the left, and 5 cm. to the right of the median line. Pulsation in the arteries of the neck. Apex beat heaving. Systolic impulse over apex. A systolic thrill can be felt to the right of the sternum. A double murmur over the apex and louder over the aortic region. Pulse 95. Moderate tension, rather slow rise and quick fall. Pistol shot in femorals. Capillary pulse.

Nov. 15, 1910, he was admitted to the hospital where he improved and after his discharge he remained well, keeping in bed, however, most of the time.

Feb. 2, 1911. When in the dispensary he had an attack of palpitation during which the pulse rate rose to 160, with great throbbing in the carotids and general cyanosis. He began to spit up pinkish frothy liquid. The attack lasted forty-five minutes. He was again admitted to the house, where the diagnosis of chronic endocarditis, mitral insufficiency and aortic insufficiency, was made. He suffered from occasional attacks of tachycardia and shortness of breath. The blood-examination showed hemoglobin 90 per cent. He was discharged July 5, 1911, "improved."

July 14, 1911, he had an attack in the dispensary. There was great pain referred to the right infrascapular region. He received morphin (grain ⅛) and atropin sulphate (gr. 1/300) hypodermically to relieve and calm him, and fifteen minutes later the blood flow in his hands was measured. Pulse (sitting) 140. Hands in bath at 3:01 p. m., in calorimeters at 3:11½. Mouth temperature 38.15 C. At 3:21 p. m. left hand was put into water at 8 C.

TABLE 12.—Calorimetric Measurements in Case of Joseph Z.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
3:11	29.87	29.905	.....	3:27	30.59	
3:12	29.88	29.915	.....	3:28	30.60	Pulse 132.
3:13	29.91	29.93	.....	3:29	30.635	
3:14	29.98	29.97	.....	3:30	30.695	At 3:30 put left hand in water at 43 C.
3:15	30.07	30.04	28.1	3:31	30.735	
3:16	30.13	30.10	.....	3:32	30.775	Room 28.4 C.
3:17	30.21	30.13	.....	3:33	30.81	
3:18	30.22	30.15	.....	3:34	30.87	
3:19	30.27	30.20	.....	3:35	30.895	
3:20	30.29	30.22	.....	3:36	30.93	
3:21	30.32	30.235	.....	3:37	30.975	Room 28.3 C.
3:22	30.34	.....	.....	3:38	31.01	3:38 hand out calorimeter.
3:23	30.37	30.22	.....	3:38½		Temp. of L. 30.16 C.
3:24	30.40	.....	.....	3:48	30.97	Pulse 120. Mouth temp. 38.45 C.
3:25	30.49	.....	28.1			
3:26	30.54	.....	.....			

Cooling of calorimeters, R., 0.04 C. in ten minutes; L., 0.06 C. in fifteen one-half minutes. Volume of right hand 406 c.c., of left 412 c.c. He is right handed. Water equivalent of calorimeters with contents, R., 3,420; L., 3,425.

He attended from time to time at the dispensary feeling pretty well for awhile, but compensation broke down again and on March 3, 1913, he had again to seek admission to Lakeside Hospital with the cardiac dulness enlarged to the left to the mid-axillary line.

In another case of aortic stenosis and insufficiency and mitral insufficiency with fair compensation at the time of the blood-flow examination in a man (Matthew K.), 42 years old, the flow was 7.20 grams per 100 c.c. per minute in the right, and 5.49 grams in the left, with room temperature 22.5 C., a flow somewhat below the normal for his age and the external temperature, although by no means remarkably small. He had no edema and no dyspnea, but he complained of pain over the heart and was getting weaker.

Mat. K., aged 42, height 5 feet, 7 inches, weight 165 pounds, a worker in a railway shop, was admitted at the dispensary Dec. 2, 1910, suffering from aortic stenosis and insufficiency and mitral insufficiency. His illness began two months before and he has been getting worse ever since. He feels chilly at times. His weakness is increasing each day and he has had to give up work. He suffers from pain over the heart, palpitation and inability to sleep. There is a probable history of rheumatic fever seven years ago. The left border of the cardiac dulness is 12½ cm. to the left of the mid-sternal line, the right border 4 cm. to the right of it, upper border at third rib. No capillary pulse, no edema, urine normal.

The blood-flow in the hands was measured Jan. 24, 1911. He has no shortness of breath. The systolic blood-pressure is 170. Mouth temperature 36.6 C.; pulse (sitting) 80. Hands in bath at 3:16 p. m.; in calorimeters at 3:27, out of calorimeters at 3:42. There was 3,050 c.c. of water in each calorimeter. Room temperature 22.0 C. before the observations were begun.

TABLE 13.—Calorimeter Measurements in Case of Mat. K.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.26	29.42	29.19	.....	3.37	29.73	29.43	....
3.28	29.40	29.18	.....	3.38	29.78	29.46	....
3.29	29.42	29.18	.....	3.39	29.82	29.48	....
3.30	29.44	29.20	.....	3.40	29.86	29.51	....
3.31	29.47	29.21	.....	3.41	29.90	29.54	....
3.33	29.54	29.29	.....	3.42	29.96	29.58	23.1
3.34	29.60	29.33	.....	3.59	29.76	29.42	....
3.35	29.64	29.37	.....	4.04	29.70	29.37	....
3.36	29.70	29.40	.....				

Cooling of calorimeters in twenty-two minutes, R., 0.26 degree; L., 0.21 degree. Volume of right hand in calorimeter 440 c.c., of left 435 c.c. He is right handed.

He continued to come to the dispensary. On Feb. 2, 1911, he complained of pain over the precordia and down the shoulder and arm. His last visit was on April 2, 1913, when his condition was not essentially altered.

In a case of mitral and tricuspid insufficiency (P. B.) with venous engorgement, edema of the ankles and fluid in the peritoneal cavity, a perfectly good flow was seen in the hands (12.80 grams per 100 c.c. per minute for the right and 13.46 grams for the left, with room temperature 25.5 C.). A fair reflex vasoconstriction was obtained by the application of cold to the contralateral hand, but the application of warmth failed to increase the flow, even to the initial level, owing no doubt to the fact that the vessels were already so much dilated. There was no dyspnea during the experiment, and the driving power of the heart with its obviously powerful stroke was adequate to maintain a normal flow through the periphery. The vasomotor centers seem to have retained their normal excitability. The cord, therefore, in spite of the venous engorgement, was not suffering appreciably at the time.

P. B., section hand on a railway, aged 31, height 5 feet, 11 inches, was admitted to the dispensary May 12, 1911, with mitral and tricuspid insufficiency. He has been ill for eighteen or nineteen months, during which time he has been unable to work. He had acute articular rheumatism nineteen months before admission, had swollen feet, enlargement of the abdomen and palpitation of the heart and was in bed six weeks. The left border of the cardiac dulness is at the midaxillary line. There is a large diffuse area of cardiac pulsation visible (positive systolic) and the framework of the chest undulates with each beat. Positive venous pulsation in both jugulars. Liver much enlarged with marked systolic pulsation. There is venous engorgement, edema of the ankles and fluid in the peritoneal cavity.

The blood-flow in the hands was measured May 12, 1912. There was no dyspnea during the examination. Pulse (sitting) 100. Mouth temperature 36.9 C. Hands put into bath at 2:29 p. m., into calorimeters at 2:39. At 2:50 p. m. left hand put into water at 8 C.

TABLE 14.—Calorimetric Measurements in Case of P. B.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
2:38	30.21	30.11	.....	2:57	31.67	
2:40	30.28	30.19	.....	2:58	31.71	
2:41	30.375	30.28	.....	2:59	31.77	
2:42	30.48	30.40	.....	3:00	31.82	Room 25.7 C.
2:43	30.59	30.495	.....	3:01	31.875	At 3:01 put left hand in water at 43.1 C.
2:44	30.68	30.61	25.5	3:02	31.91	
2:45	30.79	30.71	.....	3:03	31.97	
2:46	30.88	30.80	.....	3:04	32.02	Room 25.5 C.
2:47	30.97	30.875	.....	3:05	32.085	
2:48	31.06	30.96	.....	3:06	32.135	
2:49	31.14	31.06	25.6	3:07	32.195	
2:50	31.23	31.16	.....	3:08	32.26	
2:51	31.295	.....	.....	3:09	32.32	
2:52	31.345	.....	.....	3:10	32.38	3:10 hand out calorimeter.
2:53	31.395	.....	.....	3:10½	.....	Temp. of L. is now 30.98. Room 25.7 C.
2:54	31.475	.....	.....	3:22½	32.25	
2:55	31.545	.....	25.8	3:23½	.....	Temp. L. is now 30.88 C.
2:56	31.605	.....	.....			

Cooling of calorimeters, R., 0.13 degree in twelve one-half minutes; L., 0.28 degree in thirty-two minutes. Volume of right hand 510 c.c.; of left hand 480 c.c.

He entered Lakeside Hospital August 21, 1911. He had then neither cyanosis nor edema, but there was still fluid in the abdomen. The apparent incongruity between the distention of the abdomen, the pulsation of the liver and the great comfort of the patient was remarked. Heart dulness extends on the right to 7 cm.

from the mid-sternal line in the third interspace, on the left to the anterior axillary line in the sixth interspace. The blood examination showed 90 per cent. hemoglobin. He again entered Lakeside Hospital Nov. 2, 1911, and was discharged "improved" Feb. 20, 1912.

The large flow in P. B. contrasts with the small flow in Joseph Z., in whom the delivery of blood to the systemic vessels was seriously interfered with by the insufficiency of the aortic valve.

In Ernest M., another case of mitral insufficiency with chronic bronchitis, in a boy 14 years old, the flow was also good (12.74 grams per 100 c.c. per minute for the right hand and 12.45 grams for the left hand, with room temperature 23.4 C.). Compensation was so far established that he was able to come to the dispensary and had no dyspnea during the examination.

Ernest M., boy, aged 14, height 5 feet, 1¼ inches, was admitted at the dispensary Jan. 26, 1911, suffering from mitral insufficiency with chronic bronchitis. The fingers of both hands show well marked clubbing. He has had a cough ever since he was two years old. He still has the cough and is getting thinner. His arms are thin for his age. He gives a history of heart trouble. He has never been very strong and is not well enough to go to school. His appetite is good. Up to the present time there has never been any blood in the sputum, but on Feb. 7, 1911, he stated that since his last visit he spat some blood. The sputum examination was always negative as regards tubercle bacilli.

The hand flow was measured Jan. 26, 1911. Mouth temperature 38.2 C. Rectal temperature 38.5 C. Hands in bath at 2:56 p. m.; in calorimeters at 3:07, and out of calorimeters at 3:23. There was 3,150 c.c. of water in each calorimeter. Pulse (sitting) 116. The weather was mild with rain. Room 23.4 C.

TABLE 15.—CALORIMETRIC MEASUREMENTS IN CASE OF ERNEST M.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.06	29.71	29.68	.....	3.17	30.18	30.10	....
3.09	29.73	29.68	.....	3.18	30.24	30.16	23.4
3.10	29.77	29.72	.....	3.20	30.34	30.27	....
3.12	29.89	29.82	.....	3.21	30.40	30.33	....
3.13	29.96	29.89	.....	3.22	30.45	30.39	....
3.14	30.00	29.93	.....	3.23	30.50	30.42	23.1
3.15	30.06	29.99	.....	3.42	30.30	30.27	22.7
3.16	30.12	30.05	.....				

Cooling of calorimeters in nineteen minutes, R., 0.20 degree; L., 0.15 degree. L. was on the side of the room next to the radiator, though at a good distance from it. A small centrifuge had been started at 3:23 at the side of the room nearest to R. The difference in the rate of cooling of the calorimeters, which is decidedly greater than usual, may be thus accounted for. Volume of right hand 255 c.c., of left 240 c.c.

In another boy (Frank C.), 17 years old, with mitral stenosis and insufficiency, the flow was also quite normal in amount (11.25 grams for the right and 11.58 grams for the left hand, with room temperature 22.4

C.). Compensation was fairly established. The protocol has already been published.[6] Later he was admitted several times to Lakeside Hospital suffering from broken compensation and was discharged for the last time on March 4, 1912. He afterward died.

One of the most interesting cases was that of Albert H., since the heart underwent rapid deterioration within the period of the observations and the patient died soon after the last examination, when an autopsy was obtained. The patient was a man 31 years of age with a clinical diagnosis of mitral and tricuspid insufficiency, confirmed by the autopsy, which in addition showed pericarditis with large effusion into the pericardial sac. There was no doubt that the myocardium had suffered. The patient suffered much from dyspnea if he attempted to lie down. The flow in the right hand was 4.08 grams per 100 c.c. per minute, and in the left 4.54 grams, with room temperature 24.7 C., a distinctly subnormal flow. Reflex vasoconstriction of the hand was easy to obtain on immersion of the contralateral hand in cold water, but no reflex vasodilatation could be obtained, which agreed well with the obviously poor filling of the vessels of the hand. Ten days later he was again examined. The abdomen was now full of liquid, the legs and feet greatly swollen, the heart-sounds weak and the pulse at the wrists so weak that the heart-rate was counted with the stethoscope. The hands also had increased in size. The blood-flow in the hands was very small and what was considered significant at the time, less than half its amount at the last examination (2.0 grams for the right and 1.88 grams for the left). This was for a period of seven minutes, beginning fifteen minutes after insertion of the hands in the calorimeters. For the first fifteen minutes the flow was still less. The patient said he felt better, but the great decline in the blood-flow was remarked as an ominous symptom. He died in the hospital ten days after the last examination.

Albert H., colored hotel porter, aged 31, was admitted to the City Hospital April 3, 1912, complaining of dyspnea, cough and swelling of the extremities. He had rheumatism three weeks before admission and the legs were very painful. The edema and dyspnea began one week before admission. He has grown worse, coughs most of the time and is very tired on any exertion. The physical signs of fluid in the right pleural cavity are present. Heart dulness, upper border third rib, right border parasternal line, left border midway between nipple and anterior axillary line. The rate of the heart is rapid, the sounds feeble. There is a soft mitral systolic murmur with reduplication of the second sound. Radial pulse small and easily compressible. No fibrosis. Great edema of scrotum and prepuce, and edema of lower extremities. Albumin in urine. April 5 and April 7 the dyspnea and edema were less, the mitral murmur not so pronounced, the pulse soft and not well sustained. April 9, on which day the hand flow was first measured, the signs of an increase in the fluid in the right pleural cavity were present. The heart boundaries were the same as before and the edema was still considerable. Seven hundred and fifty c.c. of liquid was aspirated from the right thorax before the blood-flow examination. His maximum temperature on April 3 was 100.6 F. It rose gradually till April 9 when it reached 104.5 F. The systolic blood-pressure on April 5 was 152; April 7, 160; April 9, 160.

Hands in bath at 1:09 p. m., in calorimeters at 1:19. Mouth temperature 37.8 C. At 1:31 p. m. left hand put into water at 7.9 C.

TABLE 16.—Calorimetric Measurements in Case of Albert H.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
1:18	30.82	30.78	.....	1:35	31.13	
1:20	30.81	30.75	.....	1:36	31.14	
1:21	30.84	30.76	24.6	1:37	31.16	Room 24.7 C.
1:22	30.87	30.79	.....	1:39	31.19	
1:23	30.89	30.82	.....	1:40	31.195	At 1:40 left hand put in water at 43 C.
1:24	30.90	30.85	24.9	1:41	31.21	
1:25	30.96	30.90	.....	1:42	31.22	Room 24.8 C.
1:26	31.03	30.96	.....	1:43	31.23	
1:27	31.07	31.00	.....	1:44	31.245	
1:28	31.08	31.02	24.6	1:45	31.26	
1:29	31.085	31.04	.....	1:46	31.28	
1:30	31.095	31.07	.....	1:47	31.295	
1:31	31.09	31.09	.....	1:48	31.305	
1:32	31.10	.....	.....	1:49	31.325	
1:33	31.105	.....	24.5	1:50	31.33	1:50 hand out calorimeter.
1:34	31.115	.....	.....	1:59	31.23	Temp. of L. is 30.81 C. at 1:59.

Cooling of calorimeters, R., 0.10 degree in nine minutes; L., 0.28 degree in twenty-eight minutes. Volume of right hand 447 c.c., of left hand 450 c.c. He says he does most of his work left handed. Water equivalent of calorimeters with contents, R., 3,452; L., 3,455. Pulse (lying down) 120. Rectal temperature 39.1 C.

April 10 his maximum temperature was 103.8 F.; April 14, 103.3 F. April 17, "the dulness in the right thorax begins as high as the fifth rib posteriorly. Heart boundary is the same." Systolic blood-pressure April 16, 130; April 18, 140; April 19, 130.

Second examination of the hand flow, April 19, 1912. The abdomen now contains much liquid. The legs and feet are greatly swollen and he cannot sleep because he is unable to lie down on account of dyspnea. The heart-sounds are weak and the pulse at the wrist barely discernible. He says he feels better than before the tapping on April 9, but he seems worse than when examined after the tapping on that date. The arms and hands, according to his statement, are not swollen, but simply fat and there is no pitting. Yet measurement of the volume of the hands demonstrates an increase in their size, although the edema is not great enough to be detected by pitting. He has no fever now.

Hands in bath at 1:58 p. m.; in calorimeters at 2:09 p. m., and out of calorimeters at 2:45. At 2:35 the right hand was put into water at 42.7 C.

Cooling of calorimeters, R., 0.295 degree in twenty-eight and one-half minutes; L., 0.17 degree in eighteen and one-half minutes. Pulse 102 (counted with stethoscope). Rectal temperature 37.75 C. It was noticed that he now has piles. He never had them before. Volume of right hand in calorimeter 475 c.c., of left hand 505 c.c. Water equivalent of calorimeters with contents, R., 3,475; L., 3,499. (See Table 17.)

April 26, 1912, edema was general in the legs, arms and face. Maximum temperature 102.4 F. He died April 29. Results of necropsy: Pericarditis; 600 c.c. fluid in the pericardial sac. Mitral valve, edges thickened, insufficient. Tricuspid valve, insufficient. One thousand c.c. fluid in the abdomen. Chronic passive congestion of the liver, spleen and kidneys.

Whether the mere mechanical effect of the liquid in the pericardial sac contributed to the small flow in Albert H. at the second examination cannot of course be determined, although it is likely enough that this was a factor in addition to the weakening of the myocardium and the insufficiency of the valves. However, if the clinical diagnosis in the next case (Roman B.) be accepted, liquid may be present in considerable amount in the pericardial sac without reducing the hand flow very markedly. This patient was a man aged 22, in whom the diagnosis of mitral insufficiency and pericardial effusion was made. Blood-flow measurements in the hands were obtained on three occasions, the first on May 29, 1912, when the heart dulness was much diminished and the swelling of the legs present on admission had disappeared. The flow came out 7.61 grams per 100 c.c. per minute in the right hand and 10.59 grams in the left hand, with room temperature 22 C. He seemed fairly comfortable and had no dyspnea. On May 31, when the weather was warmer, the room temperature being 26.3 C., the flow was 8.76 grams for the right hand and 11.05 grams for the left. The average for the two hands is normal, or nearly so, and greater of course at the second examination, in accordance with the increased room temperature. He left the hospital, and after working in a foundry for two days, his legs became swollen and he had to return to the hospital on June 11 with the same

TABLE 17.—Calorimetric Measurements in Second Examination of Albert H.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.08	29.81	29.72	.....	2.28	29.66	29.59	....
2.10	29.74	29.67	.....	2.29	29.675	29.61	....
2.11	29.72	29.65	22.7	2.30*	29.685	29.62	....
2.12	29.705	29.635	.....	2.31	29.68	29.61	....
2.13	29.695	29.625	.....	2.32	29.69	29.625	....
2.14	29.69	29.62	.....	2.33	29.695	29.63	....
2.15	29.68	29.61	.....	2.34	29.70	29.63	....
2.16	29.67	29.60	22.5	2.35	29.705	29.635	....
2.17	29.665	29.595	.....	2.36	.....	29.63	....
2.18	29.65	29.58	.....	2.37	.....	29.635	23.5
2.19	29.64	29.575	.....	2.38	.....	29.635	....
2.20	29.635	29.565	22.6	2.39	.....	29.645	....
2.21	29.63	29.56	.....	2.40	.....	29.65	....
2.22	29.625	29.555	.....	2.41	.....	29.655	....
2.23	29.62	29.55	.....	2.42	.....	29.655	....
2.24	29.62	29.55	.....	2.43	.....	29.66	....
2.25	29.63	29.56	.....	2.44	.....	29.665	....
2.26	29.64	29.57	22.7	2.45	.....	29.67	....
2.27	29.65	29.58	.....	3.03½	29.41	29.49	....

* Here the bringing in of the warm water attracted his attention. In excitable patients this may cause a change in the flow.

symptoms of broken compensation which he had at first, dyspnea, cough, greatly increased area of cardiac dulness and the edema already mentioned. On June 13 his hand flow was again examined, and came out only 5.52 grams per 100 c.c. per minute for the right hand and 8.74 grams for the left, with room temperature 21.8 C., a considerable smaller flow than at the first examination, although the external temperature was practically the same. The flow, then, concomitantly with the cardiac breakdown, has been decidedly diminished. The marked inequality in the flow in the two hands persists throughout, although the relative difference is greater at the third than at the other two examinations. No local difference in the hands or arms could be discovered to account for the difference in the flows. It is possible that it is connected with intrathoracic changes not taken account of in the diagnosis. The question of differences of flow in the two hands associated with unilateral changes in the lungs and pleurae will be taken up in a future paper.

Roman B., a laborer, aged 22, was admitted to the City Hospital May 17, 1912. He had rheumatism for the first time three years before admission. He has a typical cardiorenal facies. He seems fairly comfortable, with no dyspnea. The heart presents a pear-shaped area of dulness, left border in the mid-axillary line, right border one to three fingers' breadth to the right of the mid-sternal line, making an obtuse cardiohepatic angle. The cardiac dulness is increased when he leans forward. There is a loud systolic murmur at the apex. The second sound in the pulmonic area is split. The sounds are distant. Pulse regular in rhythm, of fair volume, rather rapid rise, and well sustained. Liver three fingers' breadth below costal margin; hard, sharp edge, not tender. Edema of legs. Urine negative.

TABLE 18.—CALORIMETRIC MEASUREMENTS IN CASE OF ROMAN B.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.21	31.03	31.05	21.4	3.32	31.52	31.68	....
3.23	31.08	31.09	.....	3.33	31.56	31.74	22.2
3.24	31.12	31.15	21.5	3.34	31.58	31.77	....
3.25	31.19	31.23	.....	3.35	31.60	31.825	22.6
3.26	31.23	31.315	.....	3.36	31.64	31.89	....
3.27	31.28	31.36	.....	3.37	31.68	31.94	22.8
3.28	31.30	31.42	.....	3.38	31.705	31.98	....
3.29	31.36	31.47	21.0	3.39	31.735	32.025	22.5
3.30	31.42	31.56	.....	3.52	31.555	.....	....
3.31	31.48	31.64	21.5	3.52½	.....	31.83	....

Cooling of calorimeters, R., 0.18 degree in thirteen minutes; L., 0.195 degree in thirteen one-half minutes. Volume of right hand 454 c.c. of left hand 439 c.c. He is right handed. Water equivalent of calorimeters and contents, R., 3,458; L., 3,446. Pulse (sitting) 96. Rectal temperature 37.95 C.

May 25, 1912, left cardiac border just outside the nipple line. Right border one finger's breadth outside of sternal margin. Cardio-hepatic angle less obtuse. Liver one finger's breadth below costal border. Heart sounds louder and more distinct.

May 29, 1912, the flow in his hands was measured. Hands in bath at 3:12 p. m.; in calorimeters at 3:21¾, and out of calorimeters at 3:39. Mouth temperature 37.25 C.

Second examination May 31, 1912. He says his right ankle pains him now. It was painful three years ago when he had rheumatism for the first time. Hands in bath at 1:51 p. m; in calorimeters at 2:01½, and out of calorimeters at 2:20. The weather was considerably warmer than at the last examination.

TABLE 19.—Calorimetric Measurements at Second Examination of Roman B.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.01	31.04	31.03	26.2	2.12	31.52	31.65	26.2
2.03	31.04	31.06	.....	2.13	31.57	31.71	....
2.04	31.08	31.125	26.3	2.14	31.61	31.77	26.3
2.05	31.125	31.17	.....	2.15	31.67	31.85	....
2.06	31.20	31.25	26.4	2.16	31.72	31.925	26.3
2.07	31.27	31.34	.....	2.17	31.76	31.97	....
2.08	31.32	31.42	26.4	2.18	31.795	32.025	26.2
2.09	31.38	31.48	.....	2.19	31.83	32.08	....
2.10	31.42	31.54	26.3	2.20	31.88	32.13	26.2
2.11	31.48	31.60	.....	2.32	31.76	32.02	....

Cooling of calorimeters in twelve minutes, R., 0.12 degree; L., 0.11 degree. Volume of right hand 451 c.c., of left hand 445 c.c. Water equivalent of calorimeters with contents, R., 3,456; L., 3,451. Pulse (sitting) 87. Rectal temperature, 37.65 degrees.

June 12, 1912, he was readmitted to the hospital, complaining of precordial pain, dyspnea, and cough. The right leg pains him more than before. Lips cyanosed. Finger tips bluish. Edema in legs. There is a diffuse wave during systole not prominent in any one region. Limits of cardiac dulness were as follows:

Interspace	Supine Posture Distance in Cm. from Midsternal Line		Sitting Posture Distance in Cm. from Midsternal Line	
	Right Border	Left Border	Right Border	Left Border
6	9.5	16	12	17.5
5	8.0	15	9.5	15.5
4	6.5	10	6	11.0
3	4.0	7	..	....

Ausculation, with moderate pressure of stethoscope, rough systolic murmur at apex. Pulmonic second accentuated and split. Aortic second, weak. With pressure of stethoscope a soft blowing murmur is heard at apex during diastole. The sounds are reduced in intensity. Free fluid in abdomen.

June 13, 1912, third examination of the hand flow. Hands in bath at 1:58½ p. m.; in calorimeters at 2:09½, and out of calorimeters at 2:25.

TABLE 20. — Calorimeter Measurements in Third Examination of Roman B.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.09	31.145	31.06	21.4	2.20	31.345	31.47	22.0
2.11	31.13	31.07	.....	2.21	31.37	31.51	....
2.12	31.14	31.095	.....	2.22	31.385	31.545	....
2.13	31.165	31.13	21.8	2.23	31.395	31.59	22.1
2.14	31.18	31.17	.....	2.24	31.405	31.625	....
2.15	31.20	31.225	21.9	2.25	31.415	31.635	....
2.16	31.22	31.26	.....	2.34	31.28	31.51	....
2.17	31.26	31.325	22.0				
2.18	31.29	31.375	.....				
2.19	31.315	31.42	.....				

Cooling of calorimeters in nine minutes, R., 0.135 degree; L., 0.125 degree. Volume of right hand 451 c.c., of left 443 c.c. Rectal temperature 37.3 C. Water equivalent of calorimeters with contents, R., 3,456; L., 3,449.

In a case (Robert T.) diagnosed as pure aortic stenosis with perfect compensation in a man, aged 22 years, the average flow in the hands was at least equal to normal (10.45 grams per 100 c.c. per minute for the right hand and 13.97 grams for the left, with room temperature 20.3 C.). He entered the hospital not for his heart condition, but for surgical treatment.

Robert T., a railroad worker 22 years old, was admitted to the City Hospital Jan. 23, 1913, for surgical tratment (crushed toes on left foot). He had typhoid fourteen years ago; also rheumatism in the neck for several weeks when a child. Denies venereal diseases. For four years after typhoid had shortness of breath and still gets short of breath if he has to hurry up, especially if he changes the manner of his work, but not when he has become accustomed to a job and can work steadily without spurts. He is well-developed and well-nourished, no cyanosis. Boundaries of cardiac dulness one and a half finger's breadth to left of nipple line, right sternal border, third interspace. A blowing systolic murmur is heard over the entire area, but best in the aortic area where it is exceedingly

TABLE 21.—Calorimetric Measurements in Case of Robert T.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Room C.
2.52	31.22	31.13	.....	3.00	31.38	31.42	20.3
2.53	31.19	31.10	.....	3.01	31.42	31.48	....
2.54	31.205	31.12	20.1	3.02	31.47	31.54	20.4
2.55	31.215	31.15	20.1	3.03	31.515	31.59	....
2.56	31.23	31.18	.....	3.04	31.56	31.65	....
2.57	31.27	31.24	20.2	3.05	31.595	31.71	20.4
2.58	31.30	31.29	20.3	3.06	31.64	31.77	....
2.59	31.35	31.36	.....	3.27	31.28	31.41	....

loud. From time to time the murmur disappears for one beat, the apex beat becomes weak and the radial pulse vanishes, the murmur corresponding to the next beat being very loud, and the apex beat very strong. The radial sphygmogram is the typical trace of aortic stenosis, with flat top and sloping up-stroke. The heart is slow. The radial pulse shows fair volume, but to appreciate this the artery must be in a particular position as the tension is low and the arm fat. The physical examination reveals nothing abnormal elsewhere. The flow in the hands were measured Jan. 31, 1913. Hands in bath at 2:41½ p. m.; in calorimeters at 2:52½, and out of calorimeters at 3:06. He sat during the whole examination with the injured left foot lying on a stool, the left leg horizontal and the right foot down. (Table 21.)

Cooling of calorimeters in twenty-one minutes, 0.36 degree for R. and L. Volume of right hand 458 c.c., of left 452 c.c. He is mostly right handed, he says. Water equivalent of calorimeters with contents, R., 3,461; L., 3,456. Blood-pressure, left arm, systolic 105 (palpation), 103 (stethoscope), 91 (sound sharply diminished), 87 (sound gone). Rectal temperature 36.6 C.

The last cases to be described are two of mitral stenosis and insufficiency, one with good (Mary S.) and the other with only slightly broken compensation (Frank W.) at the time of the examination. In the first case, a woman, 26 years old, the flow works out at 15.74 grams per 100 c.c. per minute for the right hand and 14.26 grams for the left. Even taking into account the relatively high room temperature (26.7 C.) and the youth of the patient, these flows are, if anything, above the normal. When the blood-flow in the hands is not below the normal we are usually justified in assuming that the output of the ventricles is not less than normal. The large flow in this patient agrees well with the obviously exaggerated force of the ventricular stroke, and the absence of venous engorgement, of edema and of cyanosis. It confirms the conclusion that the increased respiratory rate at the time of the examination is a nervous affair not depending on deficient exchange in the lungs. Specimens of polygraph tracings are given in Figure 3. The *a* wave is prominent.

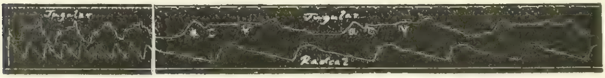

Fig. 3.—Tracings from Mary S.

Mrs. Mary S., married woman, aged 26, a Hebrew, was admitted to the City Hospital May 29, 1913, complaining of pain in the chest, weakness and shortness of breath. Seven months before admission she had an attack of acute articular rheumatism and during this attack she began to have pain in her breast. Since then there have been several short periods during which she got short of breath. There seems, however, to be a strong neurotic element in the case, and she does not look particularly ill nor does she show any marked dyspnea. She is fat and well-nourished. No cyanosis, and little, if any, edema of the legs. No venous engorgement, no pulsation in the neck. The thorax is resonant throughout. The breathing everywhere vesicular. The apex beat is in the fifth interspace below the nipple; upper border of cardiac dulness in third interspace, right border, at right sternal margin; left border two finger's breadth out. Auscultation showed the signs of mitral stenosis and insufficiency. The rather rapid breathing appears to depend largely on nervous excitement. It is certainly not associated with any signs of deficient oxygen intake. The lips are red and she is even more comfortable lying down with her head on a single pillow than sitting up.

The blood-flow in the hands was estimated June 13, 1913. The day was rather warm (external temperature about 80 F). Hands in bath at 2:28 p. m., in calorimeters at 2:40 and out of calorimeters at 2:52. Mouth temperature (two observations) 36.6 C. Pulse (sitting) 84.

TABLE 22.—Calorimetric Measurements in Case of Mary S.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Temp. Room C.
2.39	31.51	31.52	.....	2.47	31.86	31.81	26.7
2.41	31.55	31.57	26.4	2.48	31.90	31.84	....
2.42	31.60	31.60	.....	2.49	31.93	31.87	26.8
2.43	31.65	31.64	.....	2.50	31.97	31.90	....
2.44	31.71	31.68	26.5	2.51	32.01	31.94	....
2.45	31.76	31.73	.....	2.52	32.06	31.99	26.8
2.46	31.80	31.76	.....	3.07	31.89	31.83	....

Cooling of calorimeters in fifteen minutes, R., 0.17 degree; L., 0.16 degree. Volume of right hand 280 c.c., of left 259 c.c. She is right-handed. Blood-pressure, left arm, systolic 114, 95 (second phase), 62 (fourth phase), which was with practically no further fall in the pressure succeeded by the fifth phase (cessation of sound). Water equivalent of calorimeters with contents, R., 3,319; L., 3,302.

The last case is that of Frank W., a man 34 years old, with mitral stenosis and insufficiency with somewhat broken compensation, which was rapidly restored. Three examinations of the hand flow were made. The first on the day of admission, before any treatment had been given, showed a flow of 15.20 grams per 100 c.c. per minute for the right hand and 15.29 grams for the left, with the unusually high room temperature of 30.9 C. At the second examination, three days later, when the patient's clinical condition had improved, the flows were 11.95 grams for the right and 11.55 grams for the left hand, with the lower but still high room temperature of 28.5 C. The third examination, made six days after the second, with a room temperature (30.8 C.) the same as that during the first examination, showed a flow in the right hand of 11.44 grams per 100 c.c. per minute, and a flow in the left of 11.20 grams. The patient was feeling well. The re-establishment of compensation in this case was associated, then, with a diminution in the hand flow of 25 per cent. This diminution in the hand flow coincided with a reduction in the pulse-rate, quieter action of the heart and an improvement of the patient's clinical condition. It must be noted that the loss of compensation when the patient was admitted was not great, that his heart is permanently large and that there are no signs that the myocardium is, as yet, greatly impaired. The irregularity of the heart noted in the protocol is associated with premature auricular beats (Fig. 4). This condition is not included among the graver cardiac irregularities by those who have specially studied the clinical disorders of the mechanism of the heart beat. Loss of cardiac, or to speak more accurately, of cardiovascular compensation as expressed in an abnormal distribution of the blood, need not be always associated with a diminished flow through the periphery. Doubtless the abnormal distribution of the blood, resulting in engorgement of the venous side of the vascular system and a rise of venous pressure, is harmful, and is going eventually to cripple the machine. Yet it is not difficult to see that for a while the rate of the blood-flow through a part like a hand, far from being diminished, may be increased provided the driving power of the left ventricle, the aortic valves being intact, does not fail. For the rise of venous and therefore of capillary pressure may, up to a certain point, by increasing the caliber of the small vessels, favor the flow of blood. In order that this may result in increased flow through the part it is obvious that the arterial pressure must also be increased so that a sufficient slope may be maintained. And as a matter of fact, in Frank W., both the systolic and diastolic pressures in the brachial were materially higher at the first than at the second and third examinations. Corroborative evidence for the conclusion that some loss of compensation when the myocardium is not seriously affected is not incompatible for a time with a fully normal hand flow, is found in the observations on Mary S. and P. B., already referred to.

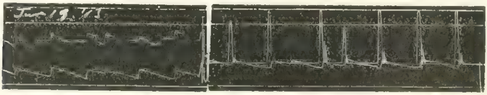

Fig. 4.—Tracings from Frank W. The left hand portion of the figure shows simultaneous tracings from the jugular bulb (upper trace) and the radial artery (lower trace). In the right hand portion of the figure simultaneous tracings from the apex (the large elevations) and the radial are given.

Frank W., an electrician aged 34, was admitted Feb. 9, 1912, to Lakeside Hospital. He says he never had rheumatism. His illness began six weeks before admission with pain all over, especially in the lumbar region and then in the epigastrium. In about a week shortness of breath came on and palpitation of the heart and he became blue in the face. A few days before admission edema was observed in the lower eyelids and the feet. The physical examination showed distended jugular veins with a systolic pulse. Heart: Apex beat in anterior axillary line in fifth interspace. Here there is a systolic impulse and thrill followed by a diastolic impact. A systolic impulse over the conus arteriosus. Left border of cardiac dulness is beyond the anterior axillary line, 18 cm. from the midsternal line, and the right border 9 cm. to right of midsternal line. The auscultatory signs are those of mitral stenosis and insufficiency. The pulse is irregular and arhythmic. Systolic blood-pressure 145, diastolic 108. Systolic pulsation of the liver. Liver dulness extends to umbilicus in right nipple line. Some edema of lower part of the back. Legs and feet edematous. When dependent, hands and feet are cyanotic. No clubbing of fingers. After a few days' rest the most prominent murmur became the presystolic rumble, heard best at the extreme apex, and indistinct elsewhere. The systolic sound was followed by a short blowing murmur, heard best to right of apex. The size and shape of the heart did not change materially. The edema rapidly disappeared. On March 6 the patient walked out of the hospital feeling well and with good cardiac compensation. The pulse rate which was 160 on admission gradually fell, and varied from 70 to 80 at the time of discharge. The minimum was 58. He broke down again after a time and was admitted to the City Hospital with the same symptoms and physical signs and was discharged improved. He was readmitted June 16, 1913. He worked for three days before he came in but was losing appetite and becoming short of breath. Some edema of the feet and ankles, but not a great deal. Slight cyanosis and dyspnea only on exertion. The point of the nose is red. The boundaries of the cardiac dulness are practically the same as those given in the physical examination at Lakeside Hospital. Pulsation in the neck veins.

The hand flow was measured June 16, 1913, a few hours after his admission and before he had had any drug treatment. The day was very warm. Pulse (sitting) 72, irregular. Hands in bath at 3:11½ p. m.; in calorimeters at 3:22¼, and out of calorimeters at 3:33.

TABLE 23.—Calorimetric Measurements in Case of Frank W.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3.22	31.49	31.49	.....	3.29	32.09	32.08	....
3.23	31.56	31.55	30.7	3.30	32.18	32.17	....
3.24	31.64	31.64	.....	3.31	32.27	32.255	....
3.25	31.72	31.72	30.8	3.32	32.355	32.34	31.0
3.26	31.82	31.82	.....	3.33	32.44	32.43	....
3.27	31.90	31.90	30.9	3.49	32.37	32.36	....
3.28	31.995	31.99	.....				

Cooling of calorimeters in sixteen minutes, 0.07 degrees.

Volume of right hand in calorimeter 456 c.c., of left hand 452 c.c. Water equivalent of calorimeter and contents, R., 3,460; L., 3,456. Blood-pressure in left brachial 133 (systolic), 103 (change in sound). Another observation 133 (systolic), 133 (change in sound). The pulse was slow and the sound diminished very rapidly to extinction after the change was heard. Rectal temperature 37.55 C.

Second examination June 19, 1913. He says he feels better. He has been receiving digitalis. There is no edema of the ankles, no dyspnea, no distention of the neck veins, no redness of the nose. The day was hot, but not so hot as that of the first examination. Hands in bath at 1:55 p. m.; in calorimeters at 2:10¼, and out of calorimeters at 2:24.

Cooling of calorimeters in twenty-three minutes, R., 0.18 degree; L., 0.16 degree. Radial pulse (sitting) 51. Volume of right hand in calorimeter 450 c.c., of left 439 c.c. Water equivalent of calorimeters with contents, R., 3,455;

L., 3446. Rectal temperature 37.75 C. Blood-pressure left arm, systolic 104, 84 (change in sound); the sound disappeared very soon after this reading. Another observation, systolic 108, 88 (change in sound followed almost at once by its complete disappearance). Pulse (sitting) 60. counted with stethoscope over apex beat. There is still arhythmia. On holding his breath the heart-rate suddenly increased considerably.

TABLE 23.—Calorimetric Measurements on Second Examination of Frank W.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.10	31.56	31.47	.....	2.18	32.09	32.02	28.3
2.11	31.61	31.53	.....	2.19	32.165	32.08	....
2.12	31.685	31.60	28.7	2.20	32.215	32.135	28.4
2.13	31.76	31.68	.....	2.21	32.295	32.20	....
2.14	31.83	31.745	28.6	2.22	32.33	32.255	28.4
2.15	31.895	31.82	.....	2.23	32.39	32.305	....
2.16	31.97	31.89	28.5	2.24	32.465	32.36	....
2.17	32.02	31.955	.....	2.47	32.285	32.20	....

Third examination, June 25, 1913. He feels well. Appetite fair, but does not sleep well. Since last examination the pulse-rate has varied between 60 and 72. The respiratory rate has rarely exceeded 20. The temperature has not exceeded 98.4 F. The day was very hot, about the same as the day of the first examination. He says his heart thumps much less than when he first came in although it gives an occasional thump. Hands in bath at 1:53 p. m.; in calorimeters at 2:04¼, and out of calorimeters at 2:19.

TABLE 24.—Calorimetric Measurements on Third Examination of Frank W.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
2.04	31.77	31.73	.....	2.13	32.32	32.26	30.85
2.05	31.78	31.74	.....	2.14	32.39	32.33	....
2.06	31.83	31.80	30.6	2.15	32.44	32.38	....
2.07	31.89	31.85	.....	2.16	32.50	32.44	30.85
2.08	31.975	31.935	30.8	2.17	32.565	32.49	....
2.09	32.04	31.995	.....	2.18	32.62	32.555	30.85
2.10	32.12	32.06	30.85	2.19	32.70	32.63	....
2.11	32.19	32.14	.....	2.35	32.62	32.555	....
2.12	32.26	32.20	.....				

Cooling of calorimeters in sixteen minutes, R., 0.08 degree; L., 0.075 degree. Volume of right hand in calorimeter 443 c.c., of left 432 c.c. Water equivalent of calorimeters with contents, R., 3,449; L., 3.440. Blood-pressure, left arm, systolic 104, 82 (change of sound followed very soon by its disappearance). Another observation. Systolic 109, 86 (change of sound). Pulse (sitting) 60, counted with stethoscope over apex. Respiration (sitting) 18. Rectal temperature 38.0 C.

SUMMARY

1. The smallest flows observed in the series of cases dealt with in this paper have been associated with marked irregularity of the heart, indicating involvement of the mechanism of the heart beat. In some of these cases the cardiac irregularity was associated with valvular lesions, but in those with the very poorest hand flows there was no evidence that the valves were involved.

2. Three cases were diagnosed as auricular fibrillation, all associated with mitral stenosis (and insufficiency). While the flow in all was below the normal it was decidedly greater in one of the patients than in the other two, although he was much the oldest of the three. This corresponded well with his clinical condition, which was good at the time of the examination, better than that of the other two patients. The ventricle in spite of its irregular action was on the whole beating fairly strongly, and was obviously delivering on the average of its beats, a fair amount of blood to the periphery.

3. In a case of mitral stenosis and insufficiency and tricuspid insufficiency, in which the heart showed marked arhythmia in part associated with the respiration (sinus arhythmia) the hand flow was also much below the normal.

4. Abnormally small flows were seen in a number of cases diagnosed as myocarditis with regular action of the heart, but feeble heart sounds not accompanied by murmurs.

5. In some cases diagnosed as myocarditis without valvular lesion, in which a serious clinical condition had previously existed, very fair hand flows, not much inferior to the normal, were found when the clinical condition had markedly improved.

6. In several cases of mitral insufficiency with good compensation and no signs of impairment of the myocardium, the hand flow was found to be quite up to the normal amount. In one case of mitral stenosis and insufficiency the flow appeared to be even somewhat greater than normal as if the big, well-compensated heart were discharging more than the usual quantity of blood.

7. In a case of mitral insufficiency with broken compensation, venous engorgement and edema, but no dyspnea or cyanosis, the hand flow was quite up to normal. In another case with the same lesions where there was little edema, no shortness of breath except on exertion, and none at the time of examination, the flow was also little if at all inferior to the normal flow, and the re-establishment of compensation was associated with an actual moderate diminution in the hand flow.

8. In a case of mitral insufficiency with physical signs of pericardial effusion a flow not much inferior to the normal was found after the patient had been some time in the hospital and had regained compensation, and when the heart dulness had decidedly diminished. When the patient, two days after leaving the hospital, broke down again and

TABLE 25.—Data Concerning

Case	Age	Date	Pulse-Rate	Blood-Pressure	Temperature (C.) of				Volume of Hands in c.c.	
					Room	Art. Blood	Calorimeters		Right	Left
							Right	Left		
Jacob W..	59	5/ 1/11	100	190, (110)	25.0	37.1	29.92	29.93	508	486
					25.1	.....	30.16	.....	...	...
					25.1	.....	30.38	.....	...	...
James M..	60	6/27/12	87	152, 72	23.0	37.15	30.93	30.93	368	356
N. P.	27	5/12/13	70	95	23.8	36.3	31.44	31.33	298	276
Jacob S. ..	44	4/25/11	104	....	22.2	36.25	29.69	29.62	390	378
					22.6	.....	.....	29.76	...	....
					22.7	.....	.....	29.78	...	....
					22.7	.....	.....	29.83	...	....
T. F. K....	57	5/19/13	120	112, 58	24.0	36.85	31.76	31.75	444	458
Peter B....	59	4/21/11	80	....	24.5	36.45	30.17	30.14	360	320
					24.3	.....	30.50	.....	...	....
					24.3	.....	30.79	.....	...	....
Peter B...	......	5/17/11	84	....	26.6	36.5	30.63	30.43	410†	394†
					26.8	.....	30.80	.....	...	....
					26.8	.....	31.12	.....	...	...
					26.7	.....	31.46	.....	...	....
John T. ..	28	4/ 9/12	100	122	24.4	37.45	31.36	31.44	450	438
					24.3	.....	31.39	.....	...	....
James H. .	63	5/29/13	70	134, 68	23.4	36.1	31.00	30.92	418	396
		6/16/13	57	110, (80)	30.9	37.1	31.69	31.74	408	392
Joseph Z..	16	7/14/11	140	....	28.1	38.3	30.10	30.10	406	412
					28.2	.....	30.51	.....	...	....
					28.3	.....	30.85	.....	...	....
Mat K....	42	1/24/11	80	170	22.8	36.6	29.72	29.40	440	435
P. B.	31	5/12/11	100	....	25.5	36.9	30.76	30.68	510	480
					25.8	.....	31.55	.....	...	....
					25.5	.....	32.13	.....	...	....
E. M.	14	1/26/11	116	....	23.4	38.0	30.14	30.07	255	240
Frank C..	17	12/19/10	116	....	22.4	37.3	30.19	30.10	275	250
Albert H..	31	4/ 9/12	120	160	24.7	38.6	30.95	30.92	447	450
Albert H..		4/19/12	102	130	22.6	37.2	29.65	29.58	475	505
Albert H..		......	...	....	23.8	.....	.....	29.65	...	....
Roman B..	22	5/29/12	96	....	22.0	37.45	31.41	31.52	454	439
Roman B..		5/31/12	87	....	26.3	37.15	31.46	31.60	451	445
Roman B..		6/13/12	...	....	21.8	36.8	31.28	31.36	451	443
Robert T..	22	1/31/13	70	103, (91) .87	20.3	36.1	31.44	31.48	458	452
Mary S...	26	6/13/13	84	114	26.7	36.6	31.81	31.78	280	259
Frank W..	34	6/16/13	72	133, (108)	30.9	37.05	32.00	31.99	456	452
Frank W..		6/19/13	60	106, (86)	28.5	37.25	32.04	31.95	450	439
Frank W..		6/25/13	60	106, (84)	30.85	37.5	32.24	32.19	443	432

* Good compensation.

† As his hands were short the marks were put higher up on the wrists than at the previous

‡ Badly broken compensation. The results on Stephen F., Mrs. A. and J. S. W. are sum-

Blood-Flow in Author's Cases

Heat Given Off in Gram-Calories			Blood-Flow in Gm. Per Min.		Flow Per 100 c.c. of Hand Per Min.		Notes
Right	Left	In Mins.	Right	Left	Right	Left	
1,050	801	13	12.50	9.55	2.46	1.96	Myocarditis.
1.225	....	10	19.62	.....	3.86	.....	Left hand in water at 42.9 C.
805	....	7	19.03	.....	3.75	.....	Left hand in water at 11.5 C.
366	270	10	7.32	4.82	1.99	1.35	Senile heart. Arhythmia.
283	216	11	5.88	4.39	1.97	1.59	Auricular fibrillation.
545	238	11	7.69	3.63	1.97	0.96	Auricular fibrillation.
....	170	5	.....	5.82	.....	1.54	Right hand in water at 43.3 C.
....	340	4	.....	14.59	.....	3.86	Right hand in water at 43.3 C.
....	340	5	.....	11.76	.....	3.11	Right hand dried and wrapped.
1.138	1,336	9	27.60	32.34	6.21	7.06	Auricular fibrillation.*
1.180	980	9	23.19	19.17	6.44	5.99	Myocarditis.
1.636	....	10	30.51	.....	8.47	.....	Left hand in water at 42.9 C.
913	....	7	25.62	.....	7.12	.....	Left hand in water at 8 C.
2.156	1,605	10	40.81	29.38	9.95	7.46	
924	....	5	36.03	.....	8.79	.....	Five min. just preceding vasomotor test.
1,643	....	10	33.93	.....	8.28	.....	Left hand in water at 8 C.
1,130	....	9	27.69	.....	6.75	.....	Left hand in water at 43 C.
516	396	10	9.41	7.32	2.09	1.67	Mitral insufficiency.‡
362	....	8	8.29	.....	1.84	.....	Left hand in water at 42.7.
154	119	10	3.35	2.55	0.80	0.64	Mitral stenosis, insufficiency; tricusp. insufficiency; arhythmia.
1.454	1,214	10	29.86	25.16	7.31	6.41	
1,505	1,165	8	25.50	19.75	6.28	4.79	Aortic insufficiency and stenosis.‡
1,402	....	9	22.22	.....	5.47	.....	Left hand in water at 8 C.
1.197	....	..	22.31	.....	5.49	.....	Left hand in water at 43 C.
2,159	1,704	11	31.70	23.90	7.20	5.49	Aortic insufficiency and stenosis.
3.608	3,618	10	65.29	64.63	12.80	13.46	Mitral and tricusp. insufficiency.
2.627	....	11	49.60	.....	9.72	.....	Left hand in water at 8 C.
2.102	.....	9	54.40	.....	10.67	.....	Left hand in water at 43.1 C.
2.988	2,772	13	32.49	29.88	12.74	12.45	Mitral insufficiency.
2.378	2.331	12	30.96	29.97	11.25	11.58	Mitral stenosis and insufficiency.
1.380	1,555	11	18.22	20.45	4.08	4.54	Mitral and tricusp. insufficiency.‡
452	455	7	9.50	9.48	2.00	1.88	
....	472	10	.....	6.94	.....	1.37	Right hand in water at 42.7 C.
3.008	3,970	16	34.58	46.49	7.61	10.59	Mitral insuff. with pericardial effusion.
3.440	4.176	17	39.5	49.18	8.76	11.05	
1.610	2.466	13	24.92	38.74	5.52	8.74	
2.007	2.626	10	47.85	63.15	10.45	13.97	Aortic stenosis.
2.091	1.763	11	44.09	36.94	15.74	14.26	Mitral stenosis and insufficiency.
3.152	3.148	10	69.35	69.11	15.20	15.29	Mitral stenosis and insufficiency .
3.280	3.146	13	53.80	50.73	11.95	11.55	
3.359	3,237	14	50.68	48.38	11.44	11.20	

examination.

marized in a previous paper (Heart, 1911, iii, 84).

returned with some dyspnea, cough and swelling of the legs, the hand flow was found distinctly below its previous value.

9. In two cases of mitral insufficiency with badly broken compensation, with venous engorgement, edema, cyanosis and dyspnea, the hand flow was much below the normal. In one of these cases a striking diminution occurred a few days before death.

10. In a case of apparently pure aortic stenosis with perfect compensation, the hand flow was normal in amount.

11. In a case of aortic stenosis and insufficiency, with mitral insufficiency, while there were no signs of broken compensation, the hand flow was somewhat below the normal.

12. In a case of aortic insufficiency and stenosis, with badly broken compensation (great dyspnea, pulmonary edema), the hand flow was greatly diminished.

While it is obvious that some of the groups of cases are much better represented in the observations than others, as is easily understood, since they had to be collected as chance offered, certain general conclusions which, although of course at present only provisional, are yet entitled to some weight, seem to emerge with sufficient clearness. It is scarcely necessary to say that in some points these conclusions simply confirm what is found by palpation of the radial pulse. But it is by no means true that even the qualitative result of the blood-flow measurement can always be predicted from feeling the pulse.

CONCLUSIONS

1. The hand flow is more apt to be markedly deficient in cases in which there is evidence of serious impairment of the myocardium, or more comprehensively and probably more accurately, of the mechanisms on which the force and rhythm of the heart's action depend, even when valvular lesions are absent, than in cases in which gross valvular lesions exist while the heart's action is strong and orderly. This holds even when in valvular diseases clinical signs of loss of compensation are present. In aortic insufficiency the hand flow appears to be less easily maintained at the normal level and more readily to fall below it when compensation is lost than in mitral insufficiency.

2. Even where there is considerable venous engorgement in cardiac cases the flow in the hands may be little if at all diminished, provided that the myocardium is not impaired. When in a case of broken compensation the flow in the hand remains good the reestablishment of compensation may be associated with a moderate decline.

3. When in a cardiac case with broken compensation the hand flow is normal or not much diminished, the indication is that the myocardium has not as yet suffered serious impairment. A decided diminution in the course of the case may be sigiificant of impending failure of the myocardium.

A STUDY OF THE BLOOD-PRESSURE IN CHILDREN SHOWING ORTHOSTATIC ALBUMINURIA *

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In a previous communication[1] we have reported our findings in an examination of the size, shape and rate of the heart in a series of children showing orthostatic albuminuria. The results of this examination revealed certain abnormalities in cardiac function and in the configuration of the heart, as seen with the fluoroscope. As has been previously pointed out, many children who are the subjects of orthostatic albuminuria reveal clinically signs and symptoms of vasomotor instability which naturally lead one to inquire into the condition of the blood-pressure. We have, therefore, made blood-pressure determinations on a number of these children previously examined in regard to their hearts, and here wish briefly to report our findings.

Systolic and diastolic pressures were determined by the auscultatory method introduced by Korotkow, the stethoscope being held over the brachial artery at the elbow. The instrument used was the one devised by Bendick,[2] the cuff, the same as the one used with the Janeway manometer, being 12 c.c. in width. For the determination of diastolic pressure, that point was taken at which the sound heard over the artery suddenly becomes fainter. This so-called fourth phase has been shown to correspond more accurately to the true diastolic pressure than the point at which all sound disappears.[3] That the readings by the auscultatory method correspond well with those taken by older but more complicated methods has been proved,[4] but owing to its comparatively recent introduction, it has been but little used in determinations on children. A short series of blood-pressure readings taken by the auscultatory method has been quite recently published by E. Mueller;[5] but we have used as controls figures which we ourselves obtained in readings taken on a series of normal healthy boys ranging in ages from 10 to 15 years, whom we were enabled to examine through the kindness of Dr. L. B. Rosenthal. to whom we here wish to express our indebtedness.

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* From the Children's Department of Mount Sinai Hospital Dispensary.

* Submitted for publication August 2, 1913.

[1] Bass and Wessler: Heart Size and Heart Function in Children Showing Orthostatic Albuminuria, THE ARCHIVES INT. MED., 1913, xi, 403.

[2] Bendick, A. J.: Jour. Am. Med. Assn., 1911, lvi, 1873.

[3] Warfield, L. W.: THE ARCHIVES INT. MED., 1912, x, 258.

[4] Warfield, L. W.: Interstate Med Jour., 1912, xix, 856: also Goodman, E. H., and Howell, A. A.: Univ. Penn. Med. Bull., 1910-11, xxiii, 469.

[5] Mueller, E.: Ztschr. f. Kinderh., 1913, vii, Nos. 3-4.

Owing to the dependence of the albuminuria on the posture of the individual, the blood-pressure readings were taken both in the recumbent and in the upright positions, and as a further test of vasomotor competency readings were taken after a short period of exercise.

The points to be considered then are the following:

1. Do the blood-pressures (systolic, diastolic and pulse-pressures) of children showing orthostatic albuminuria differ in any way from those of normal children?

2. What is the effect of change of posture, recumbent or upright, on systolic, diastolic and pulse-pressure and how do these changes compare with those occurring in the normal child?

3. What is the effect of a short period of exercise (stair-climbing) on the blood-pressures?

4. Is it possible to correlate in any way the findings in the shape, size or rate of the heart before and after exercise with the blood-pressure reactions?

BLOOD-PRESSURE IN THE UPRIGHT POSTURE

Before proceeding to a consideration of our results, it may be well to review briefly the main findings of others in the examination of blood-pressures in normal children. In general, it may be said that both systolic and diastolic pressure increase gradually according to the age of the child. The height and weight of the individual, however, are factors of importance, for in two children of the same age the taller or heavier one will usually be found to have the higher pressure (Wolfensohn-Kriss[6]). Pressure also appears to be affected by the general hygienic surroundings, for Eminet[7] found it higher in children living under good conditions than in those dwelling in poor surroundings. Sex does not appear to influence the pressure in children. All authors are agreed that children show considerable variations in pressure, the same child giving different readings on different days though apparently under identical conditions. Salle[8] found as great a variation as 18 mm. of mercury, but others (Oppenheimer and Bauchwitz[9]) assert that 10 mm. should be considered the normal limit of variation, while Mueller found a daily variation of only 2 to 5 mm. Salle further points out that high readings frequently result from nervousness on the part of the children during examination.

In comparing the results obtained by us in children showing orthostatic albuminuria with those obtained in normal children, we have considered it best to use as controls children of corresponding heights rather than those of corresponding ages. In Table 1 are tabulated the systolic, diastolic and pulse-pressures of twenty-six children showing orthostatic albuminuria, and in parallel columns the figures for normal children of the same height. The figures for the controls of this series were obtained from the literature and were recorded by means of the palpatory method. This accounts for the fact that the figures for the diastolic pressures in the albuminurics seem abnormally low. As a result of this the pulse-pressures of these children are considerably greater than those of the controls. That this is merely the result of a different method of obtaining the readings will be apparent when Tables 2 and 3 are considered, where the pressures in both the albuminurics and control children were taken by the same (auscultatory) method.

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[6] Wolfensohn-Kriss, P.: Arch. f. Kinderh., 1910, liii, p. 332.

[7] Eminet, P. P.: Arch. f. Kinderh., 1907, xlvi, 328.

[8] Salle, V.: Jahrb. f. Kinderh., 1911, lxxiii, 273.

[9] Oppenheimer and Bauchwitz: Arch. f. Kinderh., 1905, xlii, 415.

TABLE 1.—Blood-Pressures in Cases of Orthostatic Albuminuria with Normal Controls for the Corresponding Heighths

Orthostatic Albuminurics Blood-Pressure					Normal Controls* Blood-Pressure		
Case No.	Height cm.	Systolic	Diastolic	Pulse-Pressure	Systolic	Diastolic	Pulse-Pressure
1	115	125	65	60	80- 95	70- 90	10-25
2	132	103	85	18	85-115	80-105	5-35
3	121	110	85	25	80-110	75-100	5-35
4	117	80	60	20	80- 95	70- 90	10-25
5	121	112	80	32	80-110	75-100	5-35
6	115	105	60	45	80- 95	70- 90	10-25
7	112	98	55	43	80- 95	70- 90	10-25
8	132	112	65	47	85-115	80-105	5-35
9	126	105	65	40	80-110	75-100	5-35
10	126	92	75	17	80-110	75-100	5-35
11	129	85	70	15	80-110	75-100	5-35
12	131	110	65	45	85-115	80-105	5-35
13	142	103	70	33	80-125	75-115	5-50
14	130	95	70	25	85-115	80-105	5-35
15	130	130	75	55	85-115	80-105	5-35
16	133	120	75	45	85-115	80-105	5-35
17	135	95	70	25	85-115	80-105	5-35
18	131	105	90	15	85-115	80-105	5-35
19	137	110	65	45	85-115	80-105	5-35
20	128	117	87	30	80-110	75-100	5-35
21	157	110	85	35	85-120	85-110	5-35
22	155	107	75	32	85-120	85-110	5-35
23	136	90	75	15	85-115	80-105	5-35
24	140	110	60	50	80-125	75-115	5-50
25	151	120	90	30	85-120	85-110	5-35
26	145	130	95	35	80-125	75-115	5-50

* These figures are from the literature and are obtained by the oscillatory and palpatory methods.

The systolic pressures in eighteen of the twenty-six albuminurics fall within the variations found in health. Eight of the cases, however, show an increased systolic pressure, varying from 2 to 30 mm. of mercury above the upper limit of the normal figures. A careful reexamination of these eight children, however, failed to show that they differed in any way from the remainder, either in respect to subjective symptoms or in the configuration and size of their hearts. As we pointed out in the previous paper before referred to, we are fairly sure that we have ruled out any cases of nephritis, and therefore do not believe that the increased systolic pressure is due to such disease.

Pulse-pressure varies all the way from 15 to 60, the average being 33. A comparison between pulse-pressure and pulse-rate did not show any evidently constant relationship.

We may, therefore, say that our results of pressure readings taken in the upright posture approximate closely to the figures for normal children. We may also add that though the appearance of some of the children — their loss of vasomotor tone, as evidenced by cold, clammy skin, cyanotic hands and their generally visceroptotic habitus — would lead one to expect a subnormal blood-pressure, in not a single instance did we find this to be the case.

The few figures for similar examinations to be found in the literature correspond with the results above stated. Matthes,[10] who examined twenty-one boys 14 to 17 years of age, all of whom showed "albuminuria of puberty," found normal systolic pressures. Salle,[8] in a very large number of blood-pressure determinations on various types of children, states that the few who were subject to orthostatic albuminuria did not differ in any way from the healthy ones. Finally, Fischl[11] is also inclined to deny any great variation from the normal in the blood-pressures of children showing orthostatic albuminuria, though as he suggests, his readings being a little below the normal, this may be looked on as an evidence of vasomotor instability.

BLOOD-PRESSURE ON CHANGE OF POSITION

In drawing conclusions from the behavior of the blood-pressure consequent on change of position from the recumbent to the upright or vice versa, it should be remembered that different results are obtained when the readings are made immediately after such change, than when some time has been permitted to elapse after the change of position. With this in mind, our readings were not made until an interval of five minutes had elapsed to allow the circulation to adjust itself to the altered static conditions.

In Table 2 are recorded the blood-pressures in both the upright and the recumbent positions. A comparison of the figures shows that the following changes have occurred: On standing up the systolic pressure fell in fifteen cases (average 12.5 mm.); rose in six cases (average 4 mm.); remained unchanged in five. The diastolic pressure under the same conditions fell in eleven cases (average 7 mm.); rose in ten cases (average 8.5 mm.); remained unchanged in five cases. The pulse-pressure fell in twenty-two cases (average 9 mm.); rose in two cases (average 9 mm.), and remained unchanged in two cases.

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[10] Matthes, M.: Deutsch. Arch. f. klin. Med., 1904-05, lxxxii, 605.

[11] Fischl, R.: Arch. f. Kinderh., 1909, lii, 261.

TABLE 2.—BLOOD-PRESSURES IN ORTHOSTATIC ALBUMINURICS IN THE RECUMBENT AND UPRIGHT POSITIONS

	Systolic			Diastolic			Pulse-Pressure		
Case No.	Lying Down	Standing	Difference	Lying Down	Standing	Difference	Lying Down	Standing	Difference
1	140	125	—15	75	65	—10	65	60	— 5
2	103	103	0	85	85	0	18	18	0
3	105	110	+ 5	75	85	+10	30	25	— 5
4	90	80	—10	65	60	— 5	25	20	— 5
5	110	112	+ 2	85	80	— 5	25	32	+ 7
6	120	105	—15	70	60	—10	50	45	— 5
7	92	98	+ 6	60	55	— 5	32	43	+11
8	115	112	— 3	65	65	0	55	47	— 8
9	103	105	+ 2	60	65	+ 5	43	40	— 3
10	98	92	— 6	70	75	+ 5	28	17	—11
11	98	85	—13	70	70	0	28	15	—13
12	110	110	0	65	65	0	45	45	0
13	98	103	+ 8	58	70	+12	40	33	— 7
14	115	95	—20	85	70	—15	30	25	— 5
15	140	130	—10	75	75	0	65	55	—10
16	120	120	0	80	75	— 5	40	45	+ 5
17	110	95	—15	75	70	— 5	35	25	—10
18	115	105	—10	85	90	+ 5	30	15	—15
19	105	110	+ 5	55	65	+10	50	45	— 5
20	140	117	—23	100	87	—13	40	30	—10
21	130	110	—20	70	85	+15	60	25	—35
22	123	107	—13	80	75	— 5	43	32	—11
23	100	90	—10	77	75	— 2	23	15	— 8
24	112	110	— 2	55	60	+ 5	57	50	— 7
25	120	120	0	82	90	+ 8	38	30	— 8
26	130	130	0	85	95	+10	45	35	—10

It will be seen that in our cases of orthostatic albuminuria there is no constant change in systolic or diastolic pressures on change of position. The pulse-pressure on the other hand with few exceptions was smaller in the upright position.

For a critical consideration of these results it will be necessary to inform ourselves of the data in relation to this subject which are available in the literature. Unfortunately, these disclose no unanimity of opinion, but are rather replete with contradictions. Undoubtedly some of these discrepancies are dependent on the method of blood-pressure determination used by individual investigators. This applies especially to diastolic pressures, which, when determined by the oscillatory method, as has been heretofore the case, are subject to wide variation and make deductions based on them of doubtful value.

Friedman[12] found that in the erect posture the systolic pressure falls. A similar statement occurs in the reports of Shapiro[13] and Langowoy.[14] With this, Hensen,[15] however, is not in accord, as he frequently failed to note such a change in pressure on standing. Waldvogel[16] considers a drop in systolic pressure on rising as a normal reaction within certain quantitative limits. When such a drop of pressure exceeds 10 mm. of mercury it is considered by him pathologic. Birtch and Inman[17] conclude that in healthy adults not in active training, the systolic pressure is slightly lower in the upright position, the diastolic pressure at the same time is slightly raised with the result that the pulse-pressure is smaller than in the recumbent position. Dietlen[18] regards a slight systolic fall on rising as a normal change, a slight rise, however, not being necessarily pathologic. In twenty-five normal persons he found that on change of posture in 22 per cent. the systolic pressure was unchanged; in 22 per cent. it was higher in the upright position; in 56 per cent. it was lower in the upright position. The diastolic pressure was usually increased, on an average 10.5 mm. when the upright posture was assumed. John,[19] in fifty-two cases, found the pulse-pressure on standing smaller in forty-nine and larger in three cases. Quite recently Barach and Marks[20] have reported a series of cases in which pressure readings were taken on a large number of subjects both in the horizontal and in the upright positions, the experimenters attempting at the same time to eliminate the error caused by muscular exertion in changing from one posture to the other, by placing the subject on a movable platform capable of being tilted either vertically or horizontally. From their findings these authors draw the following conclusions:

> When the element of muscular effort has been eliminated change of bodily posture from the erect to the horizontal will cause an increase in the maximum pressure, a decrease in the minimum pressure and an increase in the pulse-pressure. After five minutes in the horizontal posture when the subject is retilted to the erect posture the maximum pressure will diminish, the minimum pressure increase and the pulse-pressure diminish. It will be noted that in both instances the pulse-pressure follows the same trend as the maximum pressure. . . .

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12. Friedman: Wien. med. Jahrb., 1882. (Quoted by Dietlen.)
13. Shapiro: Wratsch, 1881. (Quoted by Dietlen.)
14. Langowoy: Deutsch. Arch. f. klin. Med., 1900, lxviii, 268.
15. Hensen: Deutsch. Arch. f. klin. Med., 1900, lxvii, 436.
16. Waldvogel: München. med. Wchnschr., 1908, No. 32.
17. Birtch and Inman: Jour. Am. Med. Assn., 1912, No. 4, 265.
18. Dietlen, H.: Deutsch. Arch. f. klin. Med., 1909, xcvii.
19. John, M.: Deutsch. Arch. f. klin. Med., 1908, xciii.
20. Barach, J. H., and Marks, W. L.: Arch. Int. Med., 1913, xi, No. 5, 485.

> Nearly all the subjects of this series respond in the same way. The most notable exception was in the "poor muscular cases." These showed a tendency to reversal of the pressure curve. From the erect to the horizontal caused in more than half the cases a decrease of the maximum pressure and an increase in the minimum pressure.

We may, with certain restrictions, extract the following conclusions from these data:

1. On change of posture, systolic pressure may rise or fall to a slight degree.

2. In the upright posture diastolic pressure is slightly higher than in the recumbent.

3. Pulse-pressure is smaller in the upright posture.

Using the Korotkow method, we have taken pressure readings of twenty-two healthy boys between the ages of 10 and 14 years. The results of this examination may be seen in Table 3 and may be summarized as follows:

TABLE 3.—INFLUENCE OF CHANGE OF POSTURE ON BLOOD-PRESSURES OF NORMAL CONTROL CHILDREN. READINGS BY THE AUSCULTATORY METHOD

	Systolic			Diastolic			Pulse-Pressure		
Case No.	Lying Down	Standing	Difference	Lying Down	Standing	Difference	Lying Down	Standing	Difference
1	117	120	+ 3	87	80	— 7	30	40	+10
2	105	102	— 3	77	78	+ 1	28	24	— 4
3	112	110	— 2	80	75	— 5	32	35	+ 3
4	100	112	+12	55	55	0	45	57	+12
5	138	140	+ 2	90	90	0	48	50	+ 2
6	135	130	— 5	80	70	—10	55	60	+ 5
7	123	123	0	73	73	0	50	50	0
8	130	120	—10	85	75	—10	45	45	0
9	165	175	+10	115	110	— 5	50	65	+15
10	140	130	—10	120	95	—25	20	35	+15
11	110	112	+ 2	82	90	+ 8	28	22	— 6
12	120	130	+10	60	75	+15	60	55	— 5
13	140	125	—15	75	87	+12	65	38	—27
14	112	120	+ 8	75	77	+ 2	37	43	+ 6
15	115	125	+10	60	70	+10	55	55	0
16	140	135	— 5	50	62	+12	90	73	—17
17	145	145	0	60	75	+15	85	70	—15
18	125	117	— 8	82	90	+ 8	43	27	—16
19	142	145	+ 3	95	85	+10	47	60	+13
20	120	115	— 5	85	90	+ 5	35	25	—10
21	162	142	—20	100	100	0	62	42	—20
22	130	125	— 5	85	80	— 5	45	45	0

In the upright position: Systolic pressure is lower in eleven cases (average 8 mm. Hg); is higher in ten cases (average 6.5 mm. Hg); is unchanged in two cases. Diastolic pressure is lower in eight cases (average 11 mm. Hg); is higher in eleven cases (average 10 mm. Hg); is unchanged in four cases. Pulse-pressure is smaller in nine cases (average 14 mm. Hg); is larger in eight cases (average 9 mm. Hg); is unchanged in four case.

From these figures it will be seen that in these normal children change of posture resulted in no constant change of the systolic, diastolic or pulse-pressures. Any of these factors may vary in either direction.

If it is assumed for purposes of argument that in orthostatic albuminuria there is some abnormality in the circulation, an assumption that is freely made by most investigators of this condition, one is not unnaturally encouraged to seek in variations in blood-pressure, especially in some alteration in pulse-pressure, some evidence of such an abnormality. Especial impetus was given to this phase of the subject by the work of Erlanger and Hooker.[21] These authors showed in their case of orthostatic albuminuria that the excretion of albumin followed closely a diminution of pulse-pressure resulting from a change of position from the recumbent to the upright. When by various mechanical means such a drop of pulse-pressure was prevented, excretion of albumin failed to take place. This association of fall of pulse-pressure with excretion of albumin led us to hope that in our cases we might find uniformly a decrease of pulse-pressure on change of position from the recumbent to the upright, or at least some evidence of unusual response to postural conditions. Our results as already given, however, do not show any such marked fall of pulse-pressure on change of position, although the figures are somewhat smaller than the controls.

This subject acquires an added interest from its relation to enteroptosis. A majority of our cases show definite stigmata of this condition, probably of congenital origin or disposition. Its significance lies in the abnormality in circulation and blood-pressure, which is supposed to result from an atonic condition of the abdominal wall. Birtch and Inman,[17] in cases of visceroptosis with relaxation of the abdominal wall, concluded that on rising, although the systolic pressure may behave in a normal manner, the diastolic pressure either remains unchanged or drops. They attribute this drop of diastolic pressure directly to a loss of support of the splanchnic circulation due to atonic abdominal musculature.

Such a reaction we have failed to find in our cases. Whatever the effects we may attribute to muscular atony in orthostatic albuminuria, it may be affirmed that a definite change of peripheral systolic, diastolic and pulse-pressure is not one of them. The muscular atony, if it has any effect at all in these cases, operates otherwise than by the production of dynamic changes in the peripheral circulation.

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[21] Erlanger and Hooker: Johns Hopkins Hosp. Rep., 1904.

In concluding this subject we wish to refer to the statement of Elliott,[22] that a drop of systolic pressure in rising is pathognomonic of cases of orthostatic albuminuria. It is scarcely necessary to say that such a drop of pressure is a normal phenomenon in many cases; and that on the other hand it does not occur with sufficient regularity to invest it with the dignity of an essential symptom.

BLOOD-PRESSURE AFTER EXERCISE

In the search for tests of heart efficiency in both organic and functional circulatory disturbances, the response of the circulatory apparatus to bodily exertion has at various times been used as an index of its capabilities. In orthostatic albuminurics, it is true, there is no question of organic heart disorder in the ordinary sense. We have indeed shown in a previous article,[1] that in many cases the hearts are undersized, abnormal in shape and in some cases have noted what may be regarded as an abnormal response on the part of the heart to increased demands on its energy. Such changes are, however, probably congenital or rather developmental in origin, and their causes lie deeper and are more involved than the ordinary causes of heart disease. It cannot be doubted, however, that functionally the cardiovascular system in these cases is not so efficient as in normal children, in proof of which witness the variety of subjective symptoms of which they so frequently complain, the commonest of which are dyspnea and palpitation occurring even after the slightest bodily exertion.

In attempting to gather some information from the literature on the relationship between blood-pressure and exercise, we are at once confronted with a variety of opinions and numerous contradictory statements. Some, as for example, Stursberg and Schmidt,[23] believe that an examination of the blood-pressure after exercise is of prognostic significance; for they say that an individual, who, after very slight bodily exercise, shows a very large rise in blood-pressure, will be more easily harmed by excessive exercise than one in whom the pressure does not rise so high. This is especially true of those who show marked irritability of their pressure and their pulse-rates. In the same way Kleissel,[24] from experiments on soldiers, concludes that neurotic individuals reveal an increase of blood-pressure and pulse-rates after exercise to a degree not shown by normal persons. As opposed to these views are the conclusions of Fantus and Staehelin,[25] who state that in healthy adults the regulation of the blood-pressure is too complicated for us to draw any conclusions

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22. Elliott, A. R.: Interstate Med. Jour., 1911, xviii, 721.
23. Stursberg and Schmidt: München. med. Wchnschr., 1913, No. 4, p. 174.
24. Kleissel, R.: Wien. med. Wchnschr., 1911, No. 28, 1810.
25. Fantus and Staehelin: Ztschr. f. klin. Med., 1910, lxx, 444.

from the behavior of the maximum and minimum pressures after exercise. Masing,[26] as the result of pressure readings on numerous subjects, decides that in general the increase in blood-pressure after work is proportional to the work done; when the work is repeated the increase is not so great. The increase after muscular exercise is in proportion to the mental effort employed, and the latter varies with practice. In young individuals pressure remains high and fairly constant during work, whereas in the aged it drops after having attained its maximum. Finally, Lowsley,[27] after conducting a series of very interesting experiments on athletes, taking systolic and diastolic pressure readings immediately and at intervals after exertion, concludes that the pressure reacts differently depending on the grade of the exercise — whether it be moderate, rapid, vigorous, fatiguing or exhausting. He believes that prolonged exercise which causes an increase in the pulse-rate also causes an increase in systolic and diastolic pressures. The systolic shows the greatest rise; hence there is an increase in the pulse-pressure which may be interpreted to mean that the heart-beats are augmented as well as accelerated. He emphasizes, as an important gauge of the circulation, the time taken for the pulse-rate and blood-pressure to return to normal after exercise. It is also of interest to note in this connection that Lowsley found albuminuria in those cases which showed small pulse-pressures.

Our method of studying the effect of exercise on the blood-pressure was a follows: The pressures were at first determined in the upright position at rest. The children were then made to run up and down three flights of stairs rapidly. The blood-pressure was then immediately taken again, never longer than one-half minute after cessation of the exercise. The need of this haste in making the second reading lies in the well-known observation that the pressure falls very rapidly within a few minutes after the exercise. Readings made after such an interval give quite different results.

Summarizing Table 4, in which we have recorded the results of our blood-pressure determinations in children showing albuminuria we find that the systolic pressure rose in eighteen cases, was unchanged in two and fell in one case. The increase in systolic pressure was as high as 35 mm. Hg. The diastolic pressure fell in thirteen cases, was unchanged in one and rose in seven cases. The greatest fall was 15 mm.; the greatest rise was 15 mm. The pulse-pressure rose in every case after exercise, the rise varying from 10 to 50 mm.

For comparison, we append in Table 5 the blood-pressure of our normal control children taken before and after exercise. When these and

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[26] Masing, E.: Deutschr. Arch. f. klin. Med., 1902, lxxiv, 253.

[27] Lowsley, O. S.: Am. Jour. Physiol., 1910-11, xxvii, 446.

TABLE 4.—BLOOD-PRESSURES IN ORTHOSTATIC ALBUMINURICS BEFORE AND AFTER EXERCISE

Systolic			Diastolic			Pulse-Pressure		
Before Exercise	After Exercise	Difference	Before Exercise	After Exercise	Difference	Before Exercise	After Exercise	Difference
105	100	— 5	65	45	—20	40	55	+15
103	105	+ 2	70	60	—10	33	45	+12
92	115	+23	75	90	+15	17	35	+18
130	130	0	95	90	— 5	35	40	+ 5
110	145	+35	85	70	—15	25	75	+50
95	113	+18	70	63	— 7	25	50	+25
80	100	+20	60	75	+15	20	25	+ 5
112	125	+13	80	80	0	32	45	+13
105	122	+17	60	68	+ 8	45	54	+ 9
85	120	+35	70	85	+15	15	35	+20
130	155	+25	75	90	+15	55	65	+10
103	106	+ 3	85	65	—20	18	41	+23
90	90	0	75	70	— 5	15	20	+ 5
120	135	+15	75	70	— 5	45	65	+20
110	113	+ 3	85	82	— 3	25	31	+ 6
95	125	+30	70	75	+ 5	25	50	+25
110	120	+10	65	67	+ 2	45	53	+ 8
98	117	+19	55	50	— 5	43	67	+23
110	115	+ 5	65	60	— 5	45	55	+10
117	125	+ 8	87	85	— 2	30	40	+10
120	155	+35	90	85	— 5	30	70	+40

TABLE 5.—BLOOD-PRESSURES IN NORMAL CONTROL CHILDREN BEFORE AND AFTER EXERCISE

Systolic			Diastolic			Pulse-Pressure		
Before Exercise	After Exercise	Difference	Before Exercise	After Exercise	Difference	Before Exercise	After Exercise	Difference
120	130	+10	80	65	—15	40	65	+25
102	135	+33	78	70	— 8	24	65	+41
110	127	+17	75	65	—10	35	62	+27
112	135	+23	55	65	+10	57	70	+13
140	165	+25	90	65	—25	50	100	+50
130	160	+30	70	60	—10	60	100	+40
123	150	+27	73	55	—18	50	95	+45
120	155	+35	75	90	+15	45	65	+20
175	175	0	110	95	—15	65	75	+10
130	140	+10	95	..	....	35	..	....
112	138	+26	90	70	—20	22	68	+46
130	150	+20	75	75	0	55	75	+20
125	180	+55	87	100	+13	38	80	+42
120	160	+40	77	65	—12	43	95	+52
125	180	+55	70	70	0	55	110	+55
135	195	+60	62	70	+ 8	73	125	+52
145	160	+15	75	50	—25	70	110	+40
117	160	+43	90	82	— 8	27	78	+51
145	180	+35	85	70	—15	60	110	+50
115	150	+35	90	100	+10	25	50	+25
142	185	+43	100	90	—10	42	95	+53
125	170	+45	80	90	+10	45	80	+35

the orthostatic albuminuria cases are compared, the following points may be noted: Both groups react qualitatively in the same manner; the systolic pressures in the orthostatic cases, however, do not increase as much as do those of the normal cases. The diastolic pressures correspond fairly well in the two series. The pulse-pressure after exercise in the cases of orthostatic albuminuria are much smaller than in the controls (as 17:44). This diminution is attributable to the difference in systolic pressures.

SUMMARY

To sum up the result of our investigation we may say that the blood-pressures of children suffering from orthostatic albuminuria differ but little from those of normal children. In spite of the apparent vasomotor insufficiency which many of these children showed, the blood-pressure reactions, both in the upright and recumbent postures and also after exercise, revealed no characteristic anomaly. Nor were we able in any way to correlate the blood-pressure findings with the findings in regard to heart shape and size or pulse-rate. Children with orthostatic albuminuria who showed marked cardiovascular symptoms could not be differentiated by means of blood-pressure tests from the remainder of the group.

These results are disappointing, for the numerous interesting hypotheses concerning the etiology of orthostatic albuminuria would lead one to suppose that the vasomotor system must be in some manner to blame for the condition, especially in view of the results obtained by Erlanger and Hooker. The relationship of lordosis of the lumbar spine to orthostatic albuminuria has also been brought into connection with an abnormal cardiovascular system, since it has been suggested that only those children react to lordosis by an excretion of albumin in whom the vasomotor system is unable to prevent congestion of the kidney. This hypothesis appears plausible, but it cannot be proved or disproved by an examination of the pressure in the peripheral vessels. All that can be said at present is that the blood-pressure in the brachial artery reacts normally, though whether or not this would apply to the blood-pressure in the renal vessels of the same case, we are unable to state.

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EXPERIMENTS TO DEVELOP A MORE WIDELY USEFUL METHOD OF BLOOD-TRANSFUSION *

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In the present discussion a comprehensive review of all methods of transfusing human blood would lead us too far from our immediate subject. It will therefore be expedient to dismiss briefly and with very general consideration those methods of transfusion which involve the direct anastomosis of blood-vessels and not to attempt to estimate their relative merits. For a detailed discussion of the difficulties and limitations of this class of operation the reader is referred to the notable work of Crile published in 1909. Since the introduction of Crile's method, other ingenious devices have been contrived to facilitate the accomplishment of transfusion by an end-to-end junction of the blood-vessels, and there have been numerous accounts of the success of these operations. Less notice, however, has been given of the failures which from time to time have occurred. From a study of the literature, and from the personal communications of those who have had experience with the different ways of performing transfusion by anastomosis, we believe that it is fair to say of such methods that they ought not to be attempted by the general practitioner; that even in the most skilful hands, the presence of some slight adverse condition may seriously interfere with the chances of success; and that in all of these methods there is no satisfactory way of measuring the amount of blood which is actually transfused.

Passing on to those methods of transfusion which depend on the agency of an intermediate receptacle, one finds, in looking over the literature, that such methods were employed many years ago with defibrinated blood, particularly as applied to battle-field surgery. Esmarch, in 1877, in his work on the treatment of the wounded in war, gave a detailed description of the method advocated by him for use in the Prussian army. He believed in using only hydrostatic pressure to carry the blood into the vein; and the illustration which he gives of his contrivance for this purpose bears a very striking resemblance to a modern salvarsan infusion apparatus. Another device of this period was Collin's transfusion apparatus, which consisted of a large funnel and a cylindrical force-pump, communicating by a check-valve with a glass reservoir. From this reservoir, which also served as an air-trap, the blood was led by a tube

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and cannula into the vessel of the recipient. Hasse about the same time employed a screw-piston syringe, and Uterhart a syringe designed to trap air-bubbles. Hürter, another contemporary surgeon, recommended a similar method for arterial transfusion. It is mentioned by Esmarch that injection into an artery of the recipient obviates the danger of overdistending the right heart, and that where a vein is used, not more than 25 gm. of blood a minute should ever be injected.

With all these methods the blood was carefully defibrinated by whipping, and Esmarch recommends two defibrinations and two filtrations to insure against the possibility of injecting coagulum. The question of asepsis was at that time, of course, considered only in the most general way.

About ten years later Esmarch, influenced by the researches of Köhler on the properties of defibrinated blood, came to the conclusion that there is a dissolving action of the fibrin ferment in defibrinated blood on the red blood-cells, and also the possibility of causing coagulative changes in the circulating blood of the recipient, and that therefore "every form of transfusion of blood is to be rejected." A few years later Köhler's work was confirmed by Edelberg and much later by Schultz. In 1900 Esmarch reiterated his condemnation of defibrinated blood and recommended intravenous saline infusion for every indication that formerly demanded transfusion. Fuld, in 1903, and Morawitz in 1905, showed that the harmful substances in defibrinated blood was changed to an apparently harmless modification if filtration from the coagula was conducted without pressure, and if the blood was kept for a short time after defibrination before being injected into the circulation.

Those who have more recently experimented with the use of homologous defibrinated blood for intravenous transfusion vary in their estimate of the value of the procedure as a therapeutic method. Morawitz, in a later communication, says that there is great danger in infusing defibrinated blood into the circulation unless ample time has been allowed for the completion of all changes which may take place in the coagulative factors. The experiments of Moldovan indicate that thirty-five minutes after defibrination is the time-limit of safety. Although Curtis and David have given intravenous injections of freshly defibrinated blood in dogs in four experiments and found it to have been safely utilized by the recipient animal, these authors are not led to advocate the method for human transfusion. Hürter asserts his belief, based on clinical results in thirty-five transfusions for pernicious anemia, that the use of fresh unaltered blood is much better than the use of defibrinated blood, especially in the aplastic type of this disease. The investigations of Pike, Guthrie and Stewart on the resuscitation of the blood, indicate that the preservation of defibrinated blood for twenty-four hours impairs the physiological functioning of the erythrocytes, and they express the belief that blood, when preserved outside the circulation, soon undergoes changes which affect its nutritive as well as its bactericidal properties. The experiments of Genou in 1901 apparently indicated that plasma had little or no bacteriolytic action *in vitro* on a variety of organisms which were destroyed by serum. This supported Metchnikoff's theory that complement is derived from the leukocytes and liberated by changes induced in them during the process of coagulation. Addis, however, has since shown that Genou did not directly compare plasma with serum, but serum from cell-free plasma with serum from blood, and concludes from his experiments with "paraffin plasma" which he obtained by a very careful technic, that complement is not derived from injured leukocytes, that there is as much complement in plasma as in serum, that it is probably present in the circulating plasma of the blood and is not a product of coagulation.

Stevens and Lee, in 1884, in the course of perfusion experiments with defibrinated blood on the frog and terrapin, demonstrated the presence of an active vasoconstricting substance in defibrinated blood which was apparently due to some product of the coagulative process. The experiments of Brodie were, however, the first to indicate that there were distinctly different vasomotor agents in plasma and in serum, the main result of his investigations being the discovery of a vasodilator substance in blood-serum acting centrally on the vasomotor system through the pulmonary branches of the vagus, which this author determined to be a protein of the albumin class, coagulable by boiling and produced during the process of clotting by some action of the corpuscles. Sollmann found that serum produces a direct vasodilator effect on the isolated kidney limited to the efferent vessels, and O'Connor determined that the vasoconstricting effect of serum was due, not to its epinephrin content, but to some substance liberated during coagulation. O'Connor's observations were later confirmed by Falta and Fleming, and the existence of such a substance was inferred by Stewart and Harvey from their finding that the serum from a patient with Addison's disease, whose adrenal remains after death yielded no suprarenin, produced as great a constrictor effect on the vessels of an isolated rabbit kidney as did normal serum.

Stewart and Harvey followed up this observation with a series of perfusion experiments showing the effects of human, dog, rabbit and sheep serum and plasma on the isolated renal vessels of the dog and rabbit, on the peripheral vessels of the rabbit and frog, and on the coronary arteries of the isolated rabbit heart, and came to the conclusion that there is: (a) a vasodilator substance in plasma and in serum which is specific for the vessels of the kidney, acting directly on the muscle coats of the arteries, which is a protein of the albumin class and is precipitated by boiling and by alcohol; (b) a vasoconstrictor substance in serum, liberated by the process of clotting of the blood, which acts on the renal vessels and also on the vessels of the limb, which is not a protein, is soluble in alcohol and resists boiling.

If these conclusions be accepted as the vasomotor effects of plasma or undefibrinated blood and of serum or defibrinated blood, it is evident that the action of the latter must be a complex resultant of opposed forces.

That a deleterious effect is produced by the presence in blood intended for transfusion of substances having such a complicated action on the vasomotor system, would be difficult to prove in any given case. But, generally speaking, it is desirable beyond peradventure that blood for transfusion should be without any alteration of normal physiological function, except where some special therapeutic effect is sought, as from specifically immunized blood. Apart from the dangers of insufficient defibrination, the chances of bacterial contamination, and the other objections just mentioned, the use of defibrinated blood seems particularly inadequate from a physiological standpoint in those cases (purpura, hemophilia, etc.) in which the potential clotting elements of the patient's blood are presumably lacking or at fault.

The transfer of fresh blood from one human being to another through the agency of an intermediate receptacle seems to have been first practiced by von Ziemssen over twenty years ago. The method described by this author required one operator and three assistants. The arm of the donor was congested by a bandage and a prominent vein at the bend of the elbow was punctured without skin incision by means of a hollow cylindrical needle and the blood was withdrawn into a 25 c.c. piston syringe. While this syringe was filling another needle was likewise introduced into the recipient's vein. The ligature was then removed from the recipient's arm and the first syringe, as soon as filled, was quickly carried over and attached to the needle in the recipient's vein and the blood slowly injected. Meanwhile a second syringe was attached to the donor's needle as soon as disconnected from the first syringe, and the same procedure repeated. A third syringe followed in the same way, the first one being meanwhile carefully washed out by an assistant. Ziemssen reported that the transfer of from 250 to 300 c.c. of blood in this manner took not longer than fifteen to twenty minutes. In his first series of seven cases he stated that he observed chills and elevations of temperature in three cases and that in one of these instances he had trouble with a clot in the recipient's needle which had to be removed. He, however, considered the method less liable to the risk of causing dangerous coagulative changes in the circulating blood than transfusion by end-to-end anastomosis or the use of defibrinated blood.

A method was recommended by Moritz in 1911 which did not materially differ from Ziemssen's, except that the needles were fitted with stop-cocks and connected with the syringe by means of an intermediate tube of glass and rubber also provided with stop-cocks. Immediately after each withdrawal or injection of blood, sterile normal salt solution was injected through the needles and the stop-cocks were closed. Strips of adhesive plaster were used to minimize as far as possible the movement of the needles while within the veins. It is mentioned by Moritz that the needles are of such fine caliber that no clots of any size could possibly be injected into the circulation. Hürter recommends Moritz's method and claims to have had success with it although he refers to it as involving a delicate technic.

More recently Lindeman has advocated a method which he has practiced successfully on children and adults in a considerable number of cases. His method differs from that of Ziemssen and of Moritz in that he has devised a special set of invaginated cylindrical cannulas, and that a dozen or more syringes of 20 c.c. capacity are employed in rapid succession to convey the blood from one cannula to the other. An improvement over the Ziemssen and Moritz technics is the avoidance of traumatizing the intima of the veins by the many abrading movements within the blood-vessel of a sharp-pointed instrument, incidental to the frequent connection and disconnection of the syringes. This feature is minimized by Lindeman in that the sharp innermost cannula of his set is withdrawn from the vein as soon as it has done its work of penetration. It should also be mentioned that all cannulas receive an internal coating of liquid paraffin before use.

As no special measures to delay or prevent clotting of the blood while in the receptacle are employed in this class of operation, success and safety necessarily depend on celerity of action in conveying the blood from the vessel of the donor to that of the recipient. Prompt and repeated washing out of the cannulas with normal salt solution is also imperative. Each syringeful of blood involves one interruption of flow, two connections to blood-vessels and two disconnections, which subjects the punctured vein-wall to a considerable amount of manipulation during the course of the transfusion. Where much blood is to be transfused by this method many syringes are required, and this makes the outlay for apparatus a matter for consideration in judging of the general usefulness of the procedure. To keep a dozen or more syringes in good working order with strict asepsis, and to have the intelligent, prompt and coordinated action of at least three operators, renders this type of operation impossible for emergency use except in a hospital, and takes it out of the hands of the general practitioner. We believe, however, that this method in its simplest application, as reported by Cooley and Vaughan, should prove a valuable resource in emergencies, where only 10 to 20 c.c. of blood are required, and an ordinary syringe with needle is the most convenient instrument at hand.

It is evident to anyone who has given it consideration that a large field of usefulness would be open to the operation of blood-transfusion if it could be performed safely, quickly and surely by anyone possessing ordinary surgical skill, and, if possible, without expert assistance.

It occurred to one of us that such a practicable method might be evolved if a satisfactory apparatus could be devised to withdraw a considerable quantity of blood at one time from a vessel of the donor and inject it into a vessel of the recipient without risk of clotting; and more particularly from a study of the recent investigations of Howell, of Duke and of Whipple on the nature and significance of the factors concerned in blood-coagulation, it seemed that there were two alternative lines of experimentation which held out some promise of overcoming the danger of clotting in blood-transfusion. These alternatives are:

(*a*) The employment of an intermediate system, providing no point of contact with any moistenable surface, and at the same time minimizing as far as possible the exposure of broken tissue surface to the blood-stream; (*b*) the employment of a sufficient amount of some physiologic agent (antithrombin), to restrain or offset the initiative factors of coagulation during the time of the conveyance of the blood through a foreign system, such as glass and metal.

The investigation of the possibilities of the second of these alternatives is already under way and will form the subject of a later communication.

It is, however, with the development of the first of these procedures that the present paper has to do; and we may say at once that this has resulted in a method of drawing blood from the donor's blood-vessel directly into a paraffin receptacle, carrying the blood to the recipient, and injecting it into the recipient's circulation in precisely the same way in which it was obtained from the donor. Excepting the air-contact of its upper surface while in the receptacle, the blood does not touch anything but paraffin during its passage. The paraffin receptacle consists of a thin film of hard paraffin, lining a firm supporting structure. The latter comprises a tubulated glass cylinder, closed at the lower end by an asbestos stopper, through which passes a metal cannula. The upper end of the cylinder passes directly into an aspirating tube containing an air-filter and terminating in a mouth-piece.

In considering the work which has already been done with paraffin-coated apparatus, we have been especially impressed with the reports of Curtis and David, and of Risley and Irving. From the findings of these investigators it seemed wise to plan some preliminary experiments to ascertain the essential requirements of a conveying system with a protective lining.

The materials which appear to have served best as anticoagulative coating agents in former experimental work[1] are the paraffins, ordinary commercial petrolatum, the neutral saponifiable oils and stearic acid. The latter seemed to possess no peculiar advantage and was rejected by us on theoretic grounds, because of the possible hemolytic effect[2] which is known to be a characteristic of some of the unsaturated fatty acids. The trial mixtures were, therefore, confined to ingredients of the first three classes. Olive oil and the expressed oil of almonds were chosen from the neutral saponifiable oils, and, when combined in proper proportions with paraffin and petrolatum, formed fairly satisfactory mixtures. The vegetable oils were, however, finally abandoned on account of their tendency to favor the growth of mold.

In judging the suitability of the paraffin mixtures, the physical qualities considered were:

1. Macroscopic smoothness and uniformity of surface, and microscopic fineness and uniformity of reticulation.

2. Cohesiveness and adhesiveness to glass, silver and asbestos when congealed.

3. Greasiness of surface, as judged by repulsion and globulation of watery fluids.

As a final test, glass tubes of 2 mm. internal diameter, coated with the mixture, were tested by aspirating a short column of blood directly from the vein of an animal, and the relative clotting-time of this blood-column was observed and compared with that in a similar tube without coating.

The combination finally adopted as the best of twenty-four mixtures tested was:

Grübper's filtered paraffin, melting point 60 to 62 C. (140 to 143.6 F.), 56 parts by weight, and pure white petrolatum, 44 parts by weight. This mixture has a melting point of 49 to 50 C. (120.2 to 122 F.).

Experiments to develop the best form of cannula and blood-receptacle were carried out as indicated in the reports of Experiments 1 to 4, inclusive. Several glass cylinders having a piston or plunger discharge were abandoned, as this type of apparatus was found difficult of control for slow delivery, uncertain in action, required the use of a third hand in effecting the transfer, and was not nearly so delicate as the simple pneumatic discharge assisted by gravity, which was afterward adopted.

Experiments with needles and cannulas for introduction into the vein led to many changes before a satisfactory method was evolved. It was found impossible to coat with paraffin a cylindrical needle and flexible connecting tube in conjunction with a glass container, so as to preserve an intact coating throughout the entire system, and at the same time provide a sufficiently wide channel for effectual aspiration and delivery. The wax mixture was, therefore, in the next experiments, used for coating the glass containers only, and oil or liquid paraffin was resorted to as a coating for the needles and tubing. This makeshift worked with moderate satisfaction on the experimental animal, but is open to at least a theoretic objection on account of the considerable amount of liquid oil which may enter the circulation, and the practical objection that with a flexible connection the whole aspirating apparatus cannot be held and the cannula directed into the vein with one hand, while the other hand of the operator is left free to fix the wall of the vein. At this stage of our investigation it became evident that it would be advantageous to devise a special cannula rigidly connected with a glass cylinder, forming a pipet. The construction of this instrument was based on several important principles which a diagram will elucidate (Fig. 1).

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[1] Bernheim, B. M.: Jour. Am. Med. Assn., 1912, lviii, 1007. Bordet and Genou: Ann. de l'Inst. Past., 1903, p. 822. Brewer and Legget: Surg., Gynec. and Obstet., 1909, ix, 293. Vincent, B.: Am. Jour. Dis. Child., 1911, i, 376.

[2] Adler, H. M.: THE ARCHIVES INT. MED., 1913, xi, 187. Hopkins, A. H.: THE ARCHIVES INT. MED., 1913, xi, 300.

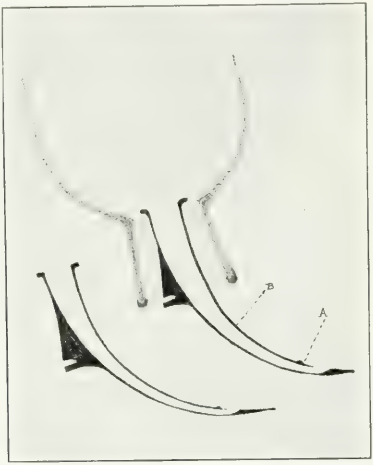

Fig. 1.—Longitudinal section of cannula seated in asbestos stopper of pipet.

The point of the instrument is conical in shape and is designed to stretch apart the tissues penetrated, while effecting the least possible injury. The distal opening of the cannula is placed laterally and the edges of this opening are smoothly rounded. The thickening or shoulder just back of the opening serves as a stop and prevents possible leakage when the cannula is pushed into the vein.

It will be seen, by reference to Figure 1 that the cylindrical part of the lumen extends for only a fraction of an inch, and then immediately widens. This enlargement, though appearing as a very gradual taper, provides an increase in the circumference proportionate to the increase of the radius, and an increase in the area of the cross-section proportionate to the squares of the radii; so that at the point *B*, which has a diameter double that of point *A*, the circumference of a contained column of fluid is only doubled, but its volume is increased four times. This means that at *B* the degree of lateral contact of the column is diminished one-half in relation to the sectional area of the column at that point.

The wall of a tube of small diameter, which can be wet by a contained fluid, necessarily determines a certain amount of lateral friction on a moving column of that fluid, the peripheral layer of the column adhering so closely to the wall of the tube as to be practically motionless. It is obvious that a paraffin coating on the wall of such a tube materially lessens this peripheral friction. That friction is also lessened by expanding the caliber of the cannula and reducing its length to a minimum, may be readily deduced from the law of Poiseuille for determining the outflow of fluid from capillary tubes. This law may be expressed by the equation:

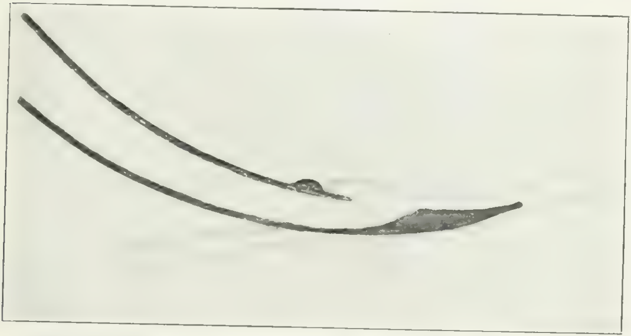

Fig. 2.—Distal end of cannula showing position in vein. Shoulder just back of opening prevents leakage from blood vessel.

$$Q = \frac{D^4 H}{L}$$

That is to say, the quantity, *Q*, which is discharged in a unit of time is directly proportional to the fourth power of the diameter, *D*, of the tube, and to the height of the pressure, *H*, and indirectly proportional to the length of the tube, *L*. It may furthermore be reasonably assumed, and there is experimental evidence to support the assumption,[3] that diminished friction of blood in a foreign system, is associated with a diminished tendency to coagulation.

The important feature of the short attachment of the cannula to the neck of the pipet is contrived by means of an air-tight asbestos stopper, enclosing the proximal end of the cannula and making the latter an arm of the pipet, the two members together forming virtually a rigid one-piece apparatus (Fig. 3).

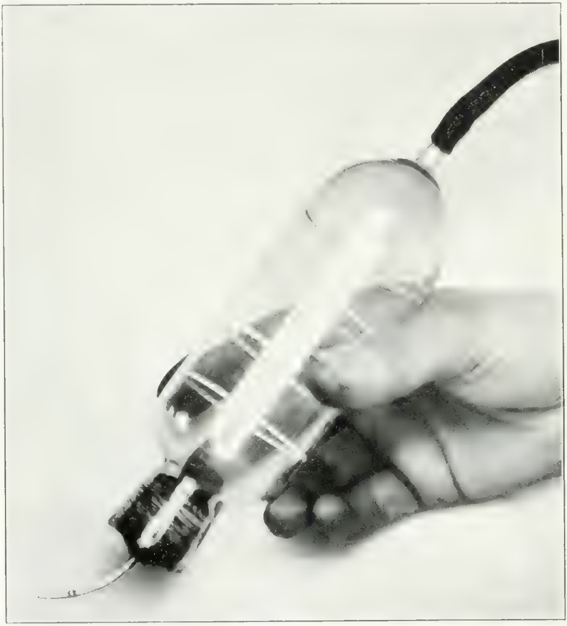

Fig. 3.—Pipet with cannula in position for insertion in vein.

METHOD OF PREPARATION AND USE OF APPARATUS

The process of coating the inside of the apparatus with paraffin requires a careful technic to be successful. The pipet must be thoroughly cleaned and free from moisture, and two coats are applied. The first coating is done at 68 to 71 C. (154.4 to 159.8 F.) in a bath containing a quantity of the paraffin mixture sufficient to allow the cylinder to be immersed for its entire length and to a depth of at least half its diameter. It is then rotated in the melted wax until uniformly heated. Air-bubbles must be avoided in the removal of the cylinder from the bath, and the coating must take place under sterile precautions. When the first coating is thoroughly hardened a sterile aspirating tube is attached, and the sterile asbestos stopper and cannula are snugly inserted (Fig. 4).

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[3] Hürthle, K.: Archiv. f. d. ges. Physiol., 1900, lxxxii, 436-438.

The second coating is applied by aspirating the hot paraffin mixture from the bath, at a temperature of 60 to 61 C. (140 to 141.8 F.) through the cannula into the cylinder. When the inflowing paraffin has reached a level of about 1 cm. above the neck of the pipet, it is immediately expelled. The cannula is then lifted from beneath the surface of the bath and its lumen quickly cleared by gentle blowing through the mouthpiece, care being taken to avoid any back suction which would result in air-bubbles. The cannula is finally protected by covering with a piece of sterile-glass tubing held in place by a strip of adhesive plaster.

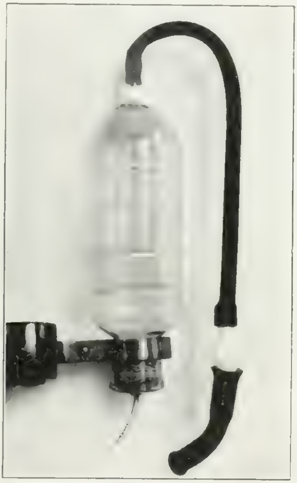

Fig. 4.—Pipet and cannula with aspirating tube and mouth-piece attached.

In warm weather the apparatus should be prepared at least one hour in advance of use so as to allow the paraffin to harden thoroughly. If a sharp cannula is used, attention must be given not to damage the point when coating the apparatus, and in every case its lumen must be smooth and clean before coating.

It should be stated here that both sharp and blunt-pointed cannulas have been used. The use of the former constitutes the simpler method of penetrating the vein when the size of the blood-vessel admits of free manipulation, but a fine probe point is to be preferred in most cases, especially if the vein is small and the danger of wounding or penetrating the opposite wall is, therefore, increased.

METHOD OF TRANSFUSION

The method of transfusing with the blunt-pointed cannula is as follows:

Instruments.—Knife, scissors, thumb forceps, fixation forceps, one or two mosquito clamps, several self-retaining stylets of different sizes (Fig. 5), sutures and needles for closing the skin wound.

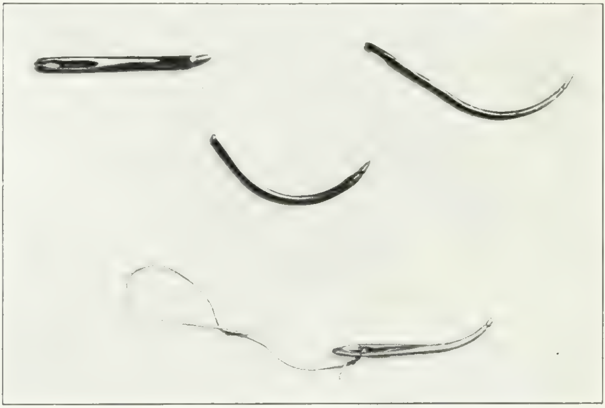

Fig. 5.—Self-retaining stylets used to puncture blood-vessel.

Apparatus.—Several prepared pipets having cannulas of the size likely to be needed for the case at hand, two obturating sleeves with clamps attached; a small tube of sterile liquid paraffin and some sterile petrolatum; a sterile aspirating tube; a cotton air-filter, and a mouth-piece.

Operation.—The donating and recipient veins are exposed under local anesthesia in the usual manner through incisions about 4 cm. in length, and the fascial sheath is cleared away so that a firm hold of the vein-wall can be secured. A pipet with a cannula suited to the size of the recipient vein is chosen, the aspirating tube with mouth-piece is attached and an obturating sleeve, with clamp attached, is dipped into sterile liquid paraffin and slipped over the cannula. The action of the sleeve is tested to make sure that it will slip easily backward and forward and it is then retracted to a position just proximal to the shoulder of the cannula. Suitable stylets are selected, dipped in sterile petrolatum, and inserted through the walls of both veins. The direction of penetration should be with the current in the recipient vein and against the current in the donating vein. The operator, having taken the mouth-piece and holding the pipet in his right hand, fixes the wall of the donating vein with a forceps in his left hand immediately beyond the point where the stylet has just been introduced, and exerts slight traction upward. The stylet is then quickly removed, by means of its attached loop, with a finger of the right hand, the traction on the vein controlling the outflow of blood; and the cannula is then pushed through the small hole which has been punctured by the stylet. The arm of the donor is now constricted above, and the blood is drawn into the pipet by aspiration. When enough blood has been obtained the cannula is withdrawn from the vein with one hand, while with the other hand the obturating sleeve is pushed to its distal position covering the mouth of the cannula a moment after it emerges from the vein. A little blood is purposely allowed to flow from the cannula at this juncture to remove any thromboplastic substance which may have been collected from the broken surface of the vessel-wall at the moment of withdrawal. The duties of an assistant, who may be the donor himself, are to remove the constriction of the arm when the blood has been obtained and to press a sterile gauze compress over the wound until it is ready for suture. Introduction of the blood into the vein of the recipient is accomplished in precisely the same way as just described for its withdrawal, except that the fourth or fifth finger of the right hand of the operator is used to retract the obturating sleeve at the moment of entering the vein.

The capacity of the pipet which has been found most useful is about 225 c.c. It is probably inadvisable to take more than 200 c.c. of blood at one time. A second pipet can be used for a second transfusion if desirable. Not more than twelve minutes should elapse in making a single transfusion with safety. One hundred and fifty c.c. should be obtained in from two to five minutes, depending on the abundance of blood-flow in the donor's arm; and this should be injected in from four to six minutes. There is probably no danger of overdistending the right auricle if delivery is effected no faster than 50 c.c. per minute for an adult, and 20 to 25 c.c. per minute for a child.

In conclusion we present, in chronologic order and as briefly as the details will permit, a report of our experiments in transfusing animals with this apparatus, together with our clinical application of the method in three cases.

EXPERIMENTAL AND CLINICAL REPORTS

Experiment 1. Feb. 12, 1913: Dog 1, male, 5.81 kg. Ether anesthesia. Femoral and external jugular veins exposed.

Apparatus: glass cylinders with asbestos-packed piston plungers; two openings at opposite ends of cylinder, one for aspiration and one for delivery. Cylinders previously coated with the plunger in position for delivery. Paraffin mixture 2. Delivery tube of rubber, 5 cm. in length, coupling the glass cylinder to an ordinary hollow needle of medium size (1.16 mm. external diameter). Delivery tube and needle not coated.

Aspiration of blood accomplished by suction with rubber bulb connected by tubing to proximal opening of cylinder provided for the purpose. When cylinder was filled with blood this opening was shut off and delivery effected by advancing the plunger. The tubing and needle were tried at first dry and then with an internal coating of oil. The blood clotted promptly in the tube and needle in the first instance, and less promptly in the tube and needle which had received the coating of oil. A much more satisfactory delivery was effected by the use of a tapered cannula with oil coating. The blood remained fluid in the paraffin-lined glass cylinders from nine to eleven minutes, the temperature of the room being about 20 C. (68 F.). The action of the plunger was found to be uncertain and difficult to control. The dog was killed at the end of the experiment.

Experiment 2.—Feb. 14, 1913: Dog 2, female, 6.34 kg. Ether anesthesia. Both femoral and external jugular veins exposed.

Apparatus: glass cylinder, about 80 c.c. capacity, previously coated with paraffin mixture No. 7, having two openings at opposite ends, one for pneumatic aspiration and expulsion of the blood, and the other for connection as in last experiment. A specially modified tapered cannula and large size (1.62 mm. external diameter) cylindrical needles were employed; cannula, needles and connecting tubes were coated with oil.

First trial (tapered cannula): 60 c.c. of blood taken from jugular and without difficulty discharged into femoral vein. The small amount of blood remaining in cylinder clotted in twelve minutes thirty seconds.

Second trial (cylindrical needle): transfusion not effected owing to clotting in needle.

Third trial (tapered cannula): 40 c.c. taken from femoral and without difficulty discharged into jugular. The small amount of blood reserved in cylinder clotted in approximately fifteen minutes. The dog was killed at the end of the experiment and the veins were dissected out and opened. No evidence of clotting was in the veins.

Experiment 3.—Feb. 15, 1913: Dog 3, male, 9.9 kg. Ether anesthesia. Aseptic precautions. Right femoral and right jugular veins exposed.

Apparatus: glass cylinder communicating directly through stopper with a specially curved and tapered cannula. The entire apparatus provided with an intact coating of paraffin mixture 9. The result of the preliminary test of the coagulation time of the dog's blood (Biffi-Brooks method) was that at 37.5 C. (99.5 F.) at the end of two minutes there was a slight fibrin formation; at two minutes forty seconds a slight fibrin formation; at four minutes a complete clot. About 48 c.c. of blood were aspirated from the jugular vein by means of a rubber bulb, an aspirating tube was clamped, the cannula withdrawn and the hole in the vein clamped with mosquito clamp and subsequently tied with fine catgut. There was considerable dripping of blood from the cannula which obscured the field of operation and required sponging with salt solution. The cannula was introduced into the exposed femoral vein in the same manner and about 45 c.c. of blood was discharged and the puncture hole tied off as before. The time of entrance of the cannula into the first vein to the withdrawal from the second vein was a little more than four minutes. Most of the blood reserved in the pipet was allowed to run out six minutes five seconds after withdrawal from the first vein, and a four-loop preparation of this was taken and transferred to the chamber of a Biffi-Brooks coagulometer with observation as follows:

Temp. 35 C. (95 F.), forty seconds; no clotting.

Temp. 34.6 C. (94.2 F.), one minute forty seconds; no clotting.

Temp. 33.2 C. (91.7 F.), four minutes thirty-five seconds; fairly firm clot.

The skin wounds were closed, collodion dressing applied and the dog allowed to come from under the anesthetic. The small amount of blood reserved in the pipet was examined at thirty-five minutes after withdrawal from the vein. That portion remaining in the cannula and in the cylinder adjacent to it was found clotted, but the larger portion which had flowed back in the cylinder as it lay in the horizontal position was still fluid. A loop of this was removed to the coagulometer and found to dissipate completely when plunged into water. The dog appeared perfectly normal after the operation and showed no subsequent ill-effects.

Clinical Trial, Case 1.—Feb. 16, 1913: E. B., a girl aged 7½, was admitted to the hospital Jan. 24, 1913, with scarlet fever, in the eighth day of her illness. Temperature 103 F., pulse 138, respiration 24; heart, lungs, abdominal organs and urine were negative on admission. The patient appeared to be making a good recovery until February 6, when she had a chill and a sudden rise of temperature to 105.8 F., and several days later developed signs of a nephritis. By February 12 she had a fully developed purpuric rash with scant bloody urine and joint pains. February 14 an uncontrollable oozing hemorrhage started from the nose, the condition of the patient became rapidly worse and a systolic heart-murmur developed. Horse-serum, 10 c.c., was given subcutaneously. February 15 the epistaxis continued: there was evidence of cardiac dilatation on percussion; vomiting of blood recurred at intervals; the hemorrhagic rash was very marked and widely distributed. Horse-serum plugs were placed in the nostrils and 20 c.c. horse-serum given subcutaneously. February 16 the patient vomited bloody fluid continually, retained no food or medication by mouth, the temperature was 98.4 F., pulse 160 and hardly perceptible at the wrist, respiration 26; a tarry stool was passed at 4 p. m.; the condition was evidently moribund. The father was summoned and offered to serve as donor for a transfusion. Apparatus similar to that in Experiment 3 was used, and 65 c.c. of blood was removed from the donor's median basilic vein and injected into the median cephalic vein of the patient. The transfer took place in approximately three and one-half minutes. No difficulty of any kind was experienced except for the dripping of blood from the cannula at the moment of entering the recipient vein, which required sponging. The small amount of blood remaining in the pipet did not clot until twenty-one minutes after withdrawal from the vein. The patient's pulse and mental condition seemed slightly better shortly after the transfusion, but death occurred early on the morning of the following day.

A condensed report of the macroscopic findings at the autopsy, performed by Dr. George P. Biggs fourteen hours after death, follows: Heart: distinct dilatation of the left ventricle, petechial hemorrhages of the endocardium and hemorrhagic areas in the papillary muscles on cross-section. Kidneys: considerably enlarged, capsules not adherent, surface smooth, pyramids and cortex both greatly swollen, cortex light in color and markings indistinct. Suprarenals: rather large, left containing a small area of softening in the upper portion, the right a small area of softening in the lower portion; no definite hemorrhages. Ulcerative lesion of the left tonsil and base of the tongue with erosion of blood-vessels. Multiple hemorrhagic areas of the lungs and spleen. Petechial areas widely distributed over skin, mucous membranes and serous membranes.

Experiment 4.—March 11, 1913: Dog 3 (the dog used in Experiment 3) Ether anesthesia. Right jugular and right femoral veins exposed.

Apparatus: A new pipet, similar to that used in last experiment, but graduated and arranged for mouth aspiration with sterile cotton air-filter. A sharp tapered cannula was used as in Experiment 3, but was cemented into an asbestos stopper. This was made by winding very thin asbestos tape, 1 inch wide, about the shank of the cannula as a core. The fiber of the asbestos was bound centrally and marginally by impregnation with a solution of sodium silicate, and medium size asbestos twine was used as an outer binding. The apparatus was coated with paraffin mixture 10.

One hundred c.c. of blood were transfused from the jugular vein to the femoral. The trnsfer was easily effected except for dripping blood when entering the second vein. The time of operation was approximately six minutes. The same amount of blood was removed from the femoral and partially discharged into the jugular; some difficulty was experienced in entering the vein due to the sharp cannula, insufficient exposure of the blood-vessel and obscuring of the field by dripping blood. The dog was killed at the end of the experiment. The same veins were used as in Experiment 3 with this dog, and necropsy showed them to be entirely patent and with no evidence of thrombosis.

Clinical Trial, Case 2.—March 16, 1913: G. S., a girl aged 10, was admitted to the hospital March 2, 1913, with severe scarlet fever of a septic type. There was a profuse nasal discharge and pronounced angina. A throat culture was negative for Klebs-Loeffler bacilli. March 5 130 c.c. of antistreptococcus serum were given without effect. The patient became rapidly worse, and on March 6, the condition being desperate, it was planned to make a transfusion with the blood of a convalescent scarlet-fever patient who volunteered for the purpose. One hundred and fifty c.c. of blood were quickly and without difficulty removed from the median basilic vein of the donor, and an attempt was made to transfuse this into the median basilic vein of the patient. This latter blood-vessel was insufficiently exposed to view and took a turn just above the upper extremity of the skin incision. Dripping of blood from the cannula further interfered with the accurate introduction of the cannula, which was a sharp one, and the vein was completely penetrated several times before its canal was finally entered. About 20 c.c. was eventually delivered, and although the blood remaining in the cannula appeared perfectly fluid, the length of time which had elapsed, about fifteen minutes, made it seem somewhat risky to continue the procedure beyond that time. A further injection of blood was therefore abandoned. The blood clotted in the cannula at about nineteen minutes, and began to clot in the cylinder at twenty-two minutes.

There was, of course, no effect to be anticipated from so small an amount of blood, and the operation had to be reckoned a failure. The patient died March 7 and no necropsy was allowed. The apparatus used in this operation was the same as noted under Experiment 4.

Experiment 5.—March 17, 1913: *To test action of cannula sleeve as an improvement in technic.*—Dog 4, male, 11.65 kg. Ether anesthesia. Aseptic precautions. Both femoral veins exposed.

Apparatus: a 200 c.c. graduated pipet with a special tapered cannula. Paraffin coating, mixture 10. An elastic cannula sleeve was contrived by using a piece of fine rubber tubing 1 cm. in length. This was held by clamping it longitudinally in a Carrel serrated clamp, and it was dipped in sterile liquid paraffin prior to use.

The right femoral vein was entered with the sleeve in position proximal to the shoulder of the cannula, and 140 c.c. of blood was aspirated as fast as could be obtained from the vein. As the cannula was removed, the sleeve was pushed into a position distal to the shoulder, thus covering the opening of the cannula. No dripping ensued. The cannula was now entered as far as the sleeve through the wall of the recipient vein, the sleeve was retracted proximally to the shoulder and the cannula pushed on into the vein up to the shoulder, allowing the escape of only a few drops of blood. One hundred and thirty-five c.c. of blood were allowed to run from the pipet by gravity assisted by gentle blowing. The time of transfer was four minutes fifteen seconds. No ligatures were necessary; the skin was sutured and a collodion dressing applied. The dog was allowed to come from under the anesthetic and made a good recovery.

Observations on the coagulation time of the blood in this experiment will be found in Table 1.

TABLE 1.—Blood Coagulation Time. Experiment 5

	Temp. C.	Time	Occurrence of Clot
Preliminary coagulation time...	37	2′ 30″	None.
	37	2′ 45″	Firm.
Blood dripping from cannula after withdrawal from vein, 7′ 35″.	37	20″	None.
	37	1′ 00″	Partial.
	37	1′ 10″	Firm.
13′ 45″	44	30″	None.
	44	1′ 15″	Partial.
	44	1′ 30″	Firm.
18′ 35″	43	1′ 00″	Very slight.
	43	1′ 45″	Partial.
	43	2′ 15″	Firm.
21′	42	1′ 00″	Partial.
	42	1′ 30″	Partial.
	42	2′ 00″	Firm.
25′ and 30′..................	Blood still dripped from cannula; coagulation time not taken.		
35′	Blood did not drip from cannula, but could be easily blown through.		

It should be noted in regard to these determinations, which were by the Biffi-Brooks method, that the loopfuls of blood obtained for observation varied considerably in volume, owing to the fact that the blood was of necessity allowed to drip from the cannula on the platinum loops, instead of being collected in the usual manner by passing the loops over the blood. This, of course, invalidates the accuracy of this method for determining the clotting time of blood dripping from the cannula. The application of the cannula sleeve in this operation was found very satisfactory and effective.

Experiment 6.—April 1, 1913: *Illustrating error of technic in coating.*—Dog 5, male, 13.6 kg. Ether anesthesia. Aseptic precautions. Both femoral veins exposed.

Apparatus: a 200 c.c. pipet and a 150 c.c. pipet provided with tapered cannulas and cannula sleeves as in Experiment 5, and coated with paraffin mixture 10. After the second coating both cannulas were briefly heated over the free flame of a Bunsen burner to reduce to a minimum the amount of wax within their lumen. (This was later recognized as an error of technic.)

A preliminary test of the dog's blood gave a coagulation time of one minute thirty-five seconds at 37 C. (98.6 F.) by the method of Dale and Laidlaw. This method was chosen as being best suited to the conditions of the investigations, and was especially satisfactory on account of the sharply defined end-point of the determination.

With the first pipet about 60 c.c. of blood were removed from the right femoral vein and injected into the left femoral vein. Clotting occurred shortly after the introduction of the cannula into the recipient vein. The clot was removed, and at eight minutes the injection was resumed, and all but a small remainder was delivered without further clotting. At nine minutes the coagulation time of the blood reserved in the pipet was one minute twenty-five seconds at 37 C. (Dale-Laidlaw).

With the second pipet a second transfusion was attempted from the right femoral to the left femoral veins, and clotting again occurred in the cannula shortly after its introduction into the recipient vein. This clot was removed, and about 80 c.c. of blood were injected into the vein at four minutes, the remainder being reserved in the pipet for observation. At eight minutes the coagulation time of blood dripping from the mouth of the canula was found to be one minute twenty-five seconds at 37 C. (98.6 F.). Between nine and ten minutes it was found that the blood had again clotted in the cannula, but that in the cylinder remained fluid for more than thirty minutes. Some of this was removed from the cylinder at thirty minutes and tested for coagulation time. It was found to be in two minutes ten seconds at 30 C. (86 F.).[4] The wounds were sutured, dressing applied and the dog allowed to come from under the anesthetic. Good recovery.

Experiment 7.—April 3, 1913: *To test the correctness of conclusions from Experiment 6 as to technic of coating.*—Dog 5, male, 13.6 kg. (dog used in experiment 6). Ether anesthesia. Aseptic precautions. Both external jugular veins used.

Apparatus: Two pipets of 120 c.c. and 200 c.c. capacity, respectively, provided with tapered cannulas, carefully coated at the proper temperatures and without flaming; paraffin coating 12.

The right jugular vein was entered against the current and about 80 c.c. of blood were removed and transferred to the left jugular vein with the current, 2 to 3 c.c. being allowed to remain in the pipet. The time of transfer was two minutes ten seconds. Preliminary coagulation time was one minute thirty seconds at 37 C. by the Biffi-Brooks method; one minute twenty seconds by the Dale and Laidlaw method at the same temperature. At sixteen minutes after removal from the vein the blood remaining in the pipet was allowed to drip from the cannula and the coagulation time was found to be one minute twelve seconds at 37 C. by the Dale-Laidlaw method.

The left jugular vein was entered with the second pipet, against the current, and 150 c.c. of blood were removed. All but 4 or 5 c.c. of this was transferred to the right jugular vein. The blood was withdrawn from the vein as rapidly as it would flow, the time being one minute forty seconds. The heart's action became coincidently very much accelerated, as also the respiration. The blood was more slowly introduced into the right jugular vein to avoid overdistention of the right auricle. The time was three minutes forty-five seconds. The amount was 145 c.c. The total time of transfer was five minutes thirty seconds. During the reintroduction of the blood the pulse and respiration fell to about the same rate as before its removal. Coagulation time of blood dripping from the cannula after the operation was as follows:

At 6 to 7 minutes after withdrawal from vein:
    1 minute 10 seconds to 1 minute 30 seconds at 37 C. by the Biffii-Brooks method.
    1 minute 10 seconds at 37 C. by the Dale-Laidlaw method.
At 18 minutes the coagulation time was 40 seconds at 37 C. by the Dale-Laidlaw method.

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[4] Corrected for temperature according to Bürker's curve for human blood[3] this would be one minute forty-four seconds at 37 C.

At 25 minutes the blood had clotted in the cannula, but was still fluid in the cylinder.

Observation of the blood remaining in the pipet was not continued after twenty-five minutes. The dog was killed at the end of the experiment. Necropsy showed a skin infection of wounds in the groins from former operation. The femoral veins used in the previous transfusion were patent and contained fluid blood.

EXPERIMENT 8.—April 7, 1913: *To test further the comparative effects of proper and improper method of second coating.*—Dog 6, male, 11 kg. Ether anesthesia.

Apparatus: same as used in the last experiment. Two pipets used. Pipet 1 received careful attention in its second coating, especially as to proper temperature (60 to 61 C.; 140 to 141.8 F.). Pipet 2 received its second coating improperly as in Experiment 6, the cannula being gently heated over a free flame to allow the excess of paraffin to be blown out.

Both femoral arteries and external jugular veins were exposed. Using Pipet 1, 200 c.c. of blood were taken from left femoral artery in one minute twenty seconds, the artery was clamped and one minute later the cannula was introduced into the left jugular vein. All but 8 c.c. of the blood was injected; time, three minutes forty seconds. Total time of transfer six minutes forty-five seconds. Preliminary clotting time of dog's freshly shed blood was one minute twenty seconds at 37 C. by the Dale-Laidlaw method. At thirty-four minutes forty-five seconds the blood reserved in the pipet for observation dripped from the cannula when the sleeve was retracted, and its coagulation time at 35.6 C. was forty seconds (Dale-Laidlaw). At forty-two minutes forty-five seconds blood still dripped from the cannula when the sleeve was retracted, and its coagulation time was 30 seconds at 35 to 36 C. (95 to 96.8 F.) by the Dale-Laidlaw method. At forty-four minutes forty-five seconds the blood had clotted in the cannula, but was still fluid in the cylinder, and remained so until sixty minutes forty-five seconds, when it had just started to clot.

With Pipet 2, 215 c.c. of blood were taken from the right femoral artery in one minute fifteen seconds, and the greater part of this was transferred to the right jugular vein. The total time was five minutes forty-five seconds. At ten minutes the blood had clotted in the lumen of the cannula. The clot was removed at fourteen minutes forty-five seconds, and the blood which then dripped away clotted in twenty seconds at 37 C. (Dale-Laidlaw). The blood again clotted in the cannula immediately, but remained fluid in the cylinder until twenty-two minutes, when it began to clot. The dog was killed at the end of the experiment.

EXPERIMENT 9.—April 16, 1913: *Illustrating effect of trauma by stretching and abrasion of intima.*—Dog 7, male, 6.6 kg. Ether anesthesia. Aseptic precautions. The same apparatus as used in Experiment 8. Preliminary coagulation time at 37 C., one minute twelve seconds by the Dale-Laidlaw method. Right femoral and saphenous veins exposed. A part of the latter was selected for entry which appeared about half the diameter of the cannula. This was, nevertheless, easily entered by stretching, and about 80 c.c. of blood were slowly aspirated. The slow withdrawal of blood was due to the small size of the vessel and the pronounced valve-action of the stretched wall against the mouth of the cannula. The cannula was removed from the saphenous vein at five minutes twenty seconds, and was then introduced into the femoral vein. No blood would pass, and the cannula was immediately withdrawn and found to contain a long clot. The clot was removed with a small forceps and the cannula again introduced into the femoral vein at nine minutes thirty seconds after entry into first vein. Half the amount of blood in the pipet, about 40 c.c., was then injected and at ten minutes ten seconds a second clot formation occurred which blocked the cannula. This was removed with difficulty, and no attempt was made to inject the blood remaining in the pipet. The vein punctures were ligated with fine catgut and the wound closed in the usual manner with a collodion dressing. The dog was allowed to come from under the anesthetic and made a good recovery.

At twelve minutes after first withdrawal from the vein the blood remaining in the pipet showed a single string of fibrin, and the blood in the cannula had again clotted. At twenty-five minutes there were several long strings of fibrin apparent on rotating the pipet, but the rest of the blood was still fluid. At thirty-four minutes a solid clot had formed.

Experiment 10.—April 22, 1913: *To confirm the conclusions from last experiment.*—Dog 7 (dog used in Experiment 9). Ether anesthesia.

Apparatus is that used in Experiment 9. Two pipets with sharp-pointed, tapered cannulas. Paraffin mixture 24.

Preliminary clotting time of dog's blood forty-six seconds at 37 C. (Dale-Laidlaw). Left femoral and internal saphenous veins exposed, also both external jugulars.

With Pipet 1 having a larger tapered cannula, about 160 c.c. were taken from the right external jugular, against the current, in two minutes ten seconds, and about one-half of this was injected, against the current, into the left external jugular in one minute thirty seconds. The total time was four minutes. No difficulty was experienced. The blood dripping from the cannula was tested as follows:

At 9 minutes 30 seconds the coagulation time was 20 to 25 seconds at 37 C.

At 34 minutes the coagulation time was 1 minute 2 seconds at 34 C. (temperature correction negligible).

At thirty-four minutes there was some fibrin formation apparent in the blood in the cylinder, although the bulk of it was perfectly fluid. At forty minutes the blood in the cannula and cylinder had clotted firmly. With Pipet 2, which was fitted with the smaller tapered cannula, the left internal saphenous vein was entered. This vessel was much smaller in its normal diameter than the cannula, and the conditions of Experiment 9 were closely simulated; that is, the distention and flapping of the vein-wall against the mouth of the cannula. Aspiration was very slow, about 50 c.c. of blood being obtained in eight minutes fifteen seconds. A very small portion of this blood (about 10 c.c.) was injected into the left jugular, and at nine minutes thirty seconds the flow was stopped by a clot in the cannula. There was also observed at this time slight evidence of fibrin formation in the fluid blood remaining in the cylinder. At nineteen minutes thirty seconds the blood in the cylinder was still fluid, but with more strings of fibrin. At thirty-two minutes the blood was still fluid, but there was much fibrin formation. Observation was not continued further. The dog was killed at the end of the experiment.

Experiment 11.—April 28, 1913: *A variation of the last two experiments to determine the effect of making the recipient vein the traumatized vessel.*—Dog 8, male, 9.5 kg. Ether anesthesia. Apparatus, two pipets as used in Experiment 10. Paraffin coating 24. Preliminary coagulation time of dog's blood one minute seventeen seconds at 39 C. (102.2 F.) by the Dale-Laidlaw method. Right femoral, left internal saphenous and both external jugular veins were exposed.

Pipet 1 was introduced into the right jugular vein and 220 c.c. of blood withdrawn in one minute forty-five seconds. One minute elapsed in transferring to the right femoral, and 200 c.c. were injected into this vessel in one minute forty-five seconds, making the total time of transfusion four minutes thirty seconds. Both tributary and recipient veins were of ample size and no hindrance was met. Observations on coagulation of the 20 c.c. of blood remaining in the pipet were as follows:

At 21 minutes 22 seconds, flowed from cannula. Fluid in cylinder, no fibrin. Coagulation time 1 minute 55 seconds, 37 C.

At 25 minutes, clotted in cannula, fluid in cylinder, with some fibrin formation.

At 35 minutes, clotted in canula, fluid in cylinder, with much fibrin formation.

At 38 minutes, clotted in cannula, firm clot in cylinder.

Pipet 2 was introduced into the left jugular vein and 200 c.c. of blood withdrawn in three minutes forty-five seconds. The internal saphenous vein selected for the recipient vessel was very small and was much traumatized and distended in effecting an entrance. When the cannula was in place it was found that the blood could not be freely injected, even with considerable pressure. At eight minutes fifteen seconds the instrument was withdrawn and another unsuccessful attempt was made to inject the same vein at a more proximal point. This also permitted too slow a delivery on account of the small size of the vessel, and at nineteen minutes the vein was penetrated at its junction with the femoral, where there was a free opportunity for discharge, and about 150 c.c. of blood were then delivered from the pipet. At twenty-three minutes thirty seconds the blood was found to have clotted in the cannula and there was considerable fibrin formation in the cylinder. At twenty-five minutes more fibrin appeared and at thirty-three minutes a firm clot existed. The dog was killed at the end of the experiment. Necropsy showed no blood-clots in the right heart or in the pulmonary arteries.

Clinical Trial, Case 3.—April 29, 1913: E. M., a boy, aged 11, had osteomyelitis of the femur with general staphylococcus septicemia, which had run a chronic course since his admission to the hospital and an operation six weeks previously. Temperature reached 102 to 103 F. daily. Hemoglobin 30 per cent. *Staphylococcus aureus* was obtained from the blood-culture. An uncle had been immunized with vaccines derived from the infecting organism of the patient for the purpose of transfusing the staphylococcus-immune blood. The donor's and recipient's median basilic veins were exposed under local anesthesia and transfusion carried out with apparatus as used in Experiment 11. One hundred and fifty c.c. of blood were removed in two minutes fifty seconds, and 100 c.c. of the amount were injected in nine minutes. The recipient's vein was unusually small. The total time was thirteen minutes fifty seconds. The blood remaining in the pipet, reserving a very little for observation, was allowed to flow on sterile gauze for local application to the suppurating sinuses. At twenty minutes there was evidence of clot formation in the cannula and a few shreds of fibrin could be seen on agitating the blood remaining in the cylinder; at twenty-six minutes there was a fairly firm clot in both cylinder and cannula. May 9, ten days later, the patient's hemoglobin was 80 per cent., temperature practically normal and local condition improved.

DISCUSSION OF RESULTS

In the preliminary part of the experimental work, that is, up to Experiment 5, the main requirements of an efficient apparatus were realized. These essential features are: (*a*) rigid pipet, arranged for pneumatic aspiration and discharge, terminating in a tapered cannula with a smoothly walled channel, the point of the cannula being conical in shape and having an opening of sufficient size to provide a rapid flow of blood; (*b*) a smooth unbroken coating of a suitable paraffin mixture throughout the apparatus; (*c*) a means of closing the opening of the cannula at will, supplied by the obturating sleeve as described in Experiment 5.

In the course of further experimentation it was found that there were several errors of technic which materially affected the success of the operation, and which by proper attention could be avoided. The first of these errors was in the matter of coating the apparatus. In Experiment 6, the clotting in the cannula was a bad feature and was evidently due to heating the cannula over the free flame after the second coating. In Experiments 7 and 8 this question was further tested and the conclusion was reached that a fairly low temperature at the second coating is essential in order to insure an intact wall of paraffin in the channel of the cannula, without which there is a tendency to clot formation in the cannula and also, to some extent, in the cylinder above.

TABLE 2.—Blood Coagulation Time in Clinical Cases 1 to 3, and Experiments 5, 7, 8, 10 and 11*

Case and Experiment No.	Time of Occurrence of Clot Formation in Cannula	Time of Occurrence of Clot Formation in Cylinder
Clinical Case 1.........	15 to 20′	21′
Clinical Case 2.........	19′	22′
Dog 4, Exp. 5..........	35′	After 35′
Dog. 5, Exp. 7.......... (Transf. B)	25′	Still fluid at 25′
Dog. 6, Exp. 8.......... (Transf. A)	44′, 45″	60′, 45″
Dog 7, Exp. 10......... (Transf. A)	34 to 40′	34 to 40′
Dog 8, Exp. 11......... (Transf. A)	25′	38′
(Transf. B)	23′, 30″	33′
Clinical Case 3.........	20′	26′

* In Table 2 are placed the results of observations on the periods of time which elapsed before coagulation of the blood in the cannula and in the cylinder in those instances in which the conditions of the experiment can be considered normal; that is to say, in which no special factors were introduced to influence an early clot formation.

It was also demonstrated in Experiment 8 that arterial blood can be very quickly obtained by this method. Whether this would usually necessitate clamping and tying of the artery, or whether the rent in the arterial wall can be repaired so as to preserve a functionating vessel as with a vein, we are, so far as our experience goes, unable to say; but we believe that the use of arterial blood may prove to be a valuable application of the method in clinical practice.

Another important error, illustrated in Experiments 9, 10 and 11, was the mistake of inviting clot formation by allowing an undue access of thromboplastic substance from stretched and broken tissue. In Experiment 9 the small donating vein was considerably stretched, and its intima was probably further damaged by flapping against the edges of the mouth of the cannula, with the result of an early and repeated clot formation. In Experiment 10 the blood from the traumatized vessel showed evidence of fibrin formation in the pipet at nine minutes thirty seconds as against thirty-four minutes in the control operation where no trauma was induced. In Experiment 11 the traumatizing of the recipient vein, on the other hand, though doubtless leading to a liberation of thromboplastin, did not produce the early clotting effect in the cannula which was observed when the donating vein was the injured vessel. The most probable explanation of this observation is that the current of outflowing blood from the cannula carried away from the instrument into the circulation, any thromboplastin which may have been formed at the site of puncture.

It is noticeable that there is a considerable range in the period of fluidity, the variation being from nineteen to forty-five minutes in the cannula, and from twenty-one to sixty minutes in the cylinder. The cause of this variation is a matter of speculation, but the most plausible explanation would seem to be that there are differences in the degree of manipulation and trauma incidental to each case, and that these differences resulted in a variation of the amount of thromboplastin set free. Among other possible factors it may be surmised that the vascular tissues of some animals are more friable than others, and that the thromboplastic substance in the tissue lymph of some individuals is more abundant or more active than in others. It should also be noted that in Dog 6, Experiment 8, Transfusion A, the comparatively long persistence of fluidity may have been due to a set of factors peculiar to this experiment, namely, that the vessel punctured was an artery, the blood arterial, and the speed with which it was obtained was very much greater than in the other experiments.

CONCLUSIONS

Generally speaking, a careful technic in the method of transfusion here described is of paramount importance, and should be based on two main principles. The first is that there shall be no lapse of the paraffin coating to act as a starting-point for the arrest and disintegration of the formed blood elements, or in whatever other way such a moistenable point may act in initiating a formation of thromboplastin. The second is that there shall be the least possible injury to the tissues of the donating vessel which are exposed directly to the transferred blood, lest there be, through such injury, an admixture of thromboplastin liberated with the tissue juices. The necessity for care in guarding against these two liabilities constitutes the one factor which militates against the simplicity and wide usefulness of the method, and it must therefore be considered a disadvantage. The practical advantages may be summed up as follows:

1. An apparatus has been contrived which is compact, which may be easily and precisely manipulated with one hand, and which may be prepared in readiness for immediate use in an emergency.

2. The operation may be easily performed by a single operator without skilled assistance, and the requisite facility in surgical technic is possessed by anyone who is able to perform an ordinary intravenous saline infusion.

3. The arrangement for pneumatic aspiration and discharge of the blood affords a delicate and convenient means of control.

4. The use of the special stylets for puncturing the exposed vein-wall insures an entrance of the cannula on the first trial, and by this method only a small skin incision is necessary. The vessels used are neither divided nor tied off and the puncture hole is very small, so that subsequent function is unimpaired.

5. The flow of blood in the donor's and the recipient's veins is not interrupted at the site of operation, and the danger of clot formation in clamped vessels is therefore not encountered.

6. The amount of blood transfused and the rate of flow can be accurately observed.

7. The donor and recipient may be separated by any convenient distance, and the risks of tearing apart are eliminated.

8. The materials of the apparatus are glass, silver and asbestos, all of which can be sterilized by dry heat in an autoclave or in an ordinary oven.

In a more extensive test of this method of transfusion under varying clinical conditions, modifications of technic may be advisable. As the aim is to perfect a method of wide usefulness to the general practitioner, there are certain improvements still to be sought in the way of greater simplicity and facility. For instance, it would be desirable to work out a means of using the apparatus safely without a double paraffin coating, or possibly to dispense with a complete coating of the cylinder by a preliminary flushing of the whole apparatus with a solution of hirudin in normal salt solution. An improvement in technic would be realized if a simple device were provided for covering the mouth of the cannula during its passage into the donor's blood-vessel, so as to afford protection from contact with broken tissue at the point of puncture. From the indications of work already done toward this end, it is not improbable that some such improvements can be worked out. Meanwhile we believe that the results of our experiments have been of sufficient interest to report, and that the method so far developed should have a more extensive clinical trial to determine its usefulness.

We wish here to express our thanks to Professor Frederic S. Lee for his kind interest in our work, and for valuable suggestions in the preparation of this paper.

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THE CONDITION OF THE BLOOD IN HEMOPHILIA, THROMBOSIS AND PURPURA *

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During the past two years I have made systematic examinations of the blood in patients suffering from various forms of diseases of the blood, hemorrhagic and thrombotic, with special reference to the variations in the amount of antithrombin and prothrombin. The most significant results have been obtained in cases of hemophilia and in so-called idiopathic or spontaneous thrombosis. The chief object of the present paper is to report the findings in these two latter conditions.

METHODS

The specimens of blood used for examination were obtained in all cases from one of the superficial veins of the arm by means of a graduated syringe (Luer form). The syringe was sterilized previously with boiling water and before inserting the needle into the vein it was filled with sterile salt solution (sodium chlorid 0.9 per cent.) by partially filling the syringe and then expelling the solution so as to leave the needle full. The object of this precaution was to avoid the bubble or two of air in the needle which otherwise interfered with the accuracy of the reading of the amount of blood taken. Usually 8 c.c. of blood were taken for each experiment and as soon as possible the portion to be examined for antithrombin and prothrombin, namely, 4 c.c., was emptied into a centrifugal tube containing 0.5 c.c. of a 1 per cent. solution of sodium oxalate (made up in a 0.9 per cent. solution of sodium chlorid). After mixing by inverting the tube this specimen was centrifugalized at a high speed to obtain a clear plasma. The plasma, which in human blood is always deeply colored, yellowish green, was pipetted off and examined as follows:

Antithrombin.—To determine the relative amount of antithrombin in the oxalated plasma of the patient it was compared always with a similar specimen taken at the same time from a normal person. The two plasmas were heated in a water-bath slowly to just 60 C. At this temperature (53 to 60) the fibrinogen is all precipitated and the thrombin and prothrombin are destroyed, while the antithrombin on the contrary is not affected, or at least is affected as little as possible consistent with the necessity of removing the fibrinogen and thrombin. Only at temperatures above 65 C. does the antithrombin show a distinct diminution in strength.

To test the antithrombin in the heated plasmas they were added in known amounts to varying mixtures of thrombin and fibrinogen. The thrombin was prepared in quantity by a method previously described[1] and was kept in dry condition in watch crystals, each crystal containing the same amount. For each test

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[1] Howell: Am. Jour. Physiol., 1910, xxvi, 453. For modification see also same, 1913, xxxii, 264.

the contents of one of these crystals was dissolved in water (4 to 8 c.c.).[2] For fibrinogen solutions I have not found it convenient to use so-called pure fibrinogen prepared by the method of Hammarsten, since it is not possible by this method to obtain solutions of uniform concentration or properties. The repeated precipitations of the fibrinogen denatures it in part. In place of such solutions I have used the oxalated and dialyzed blood plasma of dogs or cats. To get this material a fasting animal was bled into an oxalate solution. nine parts of blood to one part of a 1 per cent. solution of sodium oxalate made up in sodium chlorid, 0.9 per cent. This mixture was centrifugalized, the plasma was pipetted off and the excess of oxalate was removed by dialyzing in collodion tubes for twenty-four hours against a solution of sodium chlorid 0.9 per cent. The plasma thus obtained does not clot spontaneously, but coagulates promptly on the addition of a little thrombin. A large quantity of this material was prepared from one animal and it was dried in watch crystals, 3 to 5 c.c. to a crystal, in a current of cold air from an electrical fan. When needed the contents of one or more of these crystals was dissolved in a known amount of a 0.9 per cent. solution of sodium chlorid. The solution obtained is quite clear. In the tests described below these solutions of dried plasma will be spoken of as fibrinogen solutions. Ten drops of this solution when mixed with 2, 3, 4 and 5 drops of the thrombin solution clotted in from two to five minutes. To determine the antithrombin in the heated oxalated plasmas described above the following mixtures were made:

1. 10 drops fibrinogen sol. + 1 drop heated plasma + 2 drops thrombin solution.
2. 10 drops fibrinogen sol. + 1 drop heated plasma + 3 drops thrombin solution.
3. 10 drops fibrinogen sol. + 1 drop heated plasma + 4 drops thrombin solution.
4. 10 drops fibrinogen sol. + 1 drop heated plasma + 5 drops thrombin solution.

Inasmuch as the effect of antithrombin on thrombin varies greatly with the time allowed for their interaction it is necessary in these experiments to add first the drop of heated plasma to the 2, 3, 4 and 5 drops of thrombin solution and to allow these mixtures to stand for a definite time before adding the solutions of fibrinogen. The time interval adopted in all my experiments for this action of the antithrombin and thrombin was fifteen minutes, and care was taken to see that this interval was identical within a second or two in all comparative tests. At the expiration of the fifteen minutes the fibrinogen solution was added and the time of coagulation of each specimen was observed. The mount of antithrombin contained in one drop of heated normal plasma was sufficient, in the solutions used, to delay the action of two drops of thrombin on the fibrinogen usually for an hour or more, or to prevent clotting altogether. In the specimens containing 3, 4 and 5 drops of thrombin the delay was proportionally less marked, the specimen containing 5 drops of thrombin clotting usually in five minutes. It is easy by this method to determine the relative amounts of antithrombin in different specimens of blood. In bird's plasma or the plasma from a peptonized dog the antithrombin exists in relatively large amounts so that a drop of the heated plasma may inhibit completely the action of such amounts of thrombin as are here considered.

In determining the time of coagulation in the different specimens the tubes containing the mixtures were examined, usually at intervals of five minutes, by gently inclining the tubes. When the thrombin was in distinct excess the contents of the tubes set to a firm clot, but when the thrombin was nearly neutralized by the antithrombin it was difficult or often impossible to ascertain when clotting occurred, since under such circumstances the clot forms in several stages. First, a delicate veil which on agitation shrinks to a small membrane while later a more solid gelatinous clot may form.

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[2] The solutions of thrombin should not be filtered since the thrombin is absorbed to some extent by the filter paper.

Specimens in which the thrombin and antithrombin existed in this balanced proportion were useless for comparative purposes, and in such cases it was necessary to rely on the specimens containing more thrombin in which the clotting occurred promptly.

By way of illustration of the method, the results of one of the comparisons made between hemophilic and normal blood may be quoted.

Heated Plasma Drops	Thrombin Drops	Time Interval Minutes	Fibrinogen Drops	Coagulation Minutes
NORMAL INDIVIDUAL				
1	2	15	10	160
1	3	15	10	10
1	4	15	10	10
1	5	15	10	5
HEMOPHILIC BOY				
1	2	15	10	*
1	3	15	10	35-40
1	4	15	10	15
1	5	15	10	10

* No clot in seven hours.

This method has been applied to the examination of a very large number of specimens of human blood, normal and pathological. It has been found that while the content in antithrombin of normal blood exhibits certain fluctuations the variations are not large and do not necessarily run parallel to the coagulation time, owing to the fact that this latter time depends upon the balance between the thrombin and the antithrombin. In pathological bloods no significant constant variation in the amount of antithrombin has been detected except possibly in the condition known as idiopathic thrombosis.

Prothrombin.—In order to arrive at an idea of the relative amount or relative efficacy of the prothrombin in the plasmas examined I have adopted the procedure of adding to the oxalated plasma the optimum amount of calcium chlorid, that is to say, the amount that causes the most rapid clotting. This method was suggested by the observation that in a successful peptonized plasma (dog) addition of calcium chlorid does not cause clotting even when the plasma has been diluted previously with water. If, however, such a plasma is first oxalated and then calcium chlorid is added in proper amounts, clotting occurs readily. For some reason, not easily understood at present, the act of oxalating, that is, the decalcifying of the solution, intensifies the activation caused by the subsequent addition of calcium, so that the end result is apparently a greater production of thrombin, sufficient in fact to overcome the antithrombin and cause clotting. The alternative hypothesis that suggests itself, namely, that the process of oxalating may weaken the antithrombin, is easily shown to be erroneous. In some way the decalcification and subsequent calcification serve to bring into active form the maximum supply of prothrombin present in the blood. Whether or not this interpretation of the reaction is correct the simple procedure described has brought out a very constant and striking difference between normal and hemophilic blood. The reaction was carried out as follows: Five drops of oxalated plasma were placed in each of four tubes and to these were added in series, 2, 3, 4 and 5 drops of a 0.5 per cent. solution of calcium chlorid, with the idea that in one of the tubes the optimum concentration of calcium would be obtained. With the amount of plasma used clotting occurred first in the tubes containing 2 or 3 drops of calcium chlorid. With one drop the clotting occurred slowly or not at all, owing to an insufficiency of calcium, while in the tubes with 4 or 5 drops the clotting was somewhat slower than in the tubes with 2 or 3 drops, owing to too great an excess of calcium. Tested by this method the clotting of normal blood plasma is remarkably uniform, varying between nine and twelve minutes. In the plasmas of hemophilic blood, on the contrary, the time of clotting is greatly prolonged. This fact, indeed, has been noted by Addis,[3] although he does not seem to have used the reaction in any extensive way. I have employed the reaction, as described above, for a large series of bloods to throw light on the amount or efficacy of the prothrombin, when parallel tests have established the fact that there is no variation in the amount of antithrombin in the bloods examined.

RESULTS

Purpura.—At different times in the course of this work specimens of blood have been obtained from patients suffering from various forms of purpura, including one case of severe purpura hemorrhagica. The time of coagulation of these bloods, when obtained by venepuncture, did not vary distinctly from normal, and the content of the plasmas in antithrombin and prothrombin was also within the limits found for normal bloods. It does not seem desirable at present to publish the details of these negative findings, since this paper deals especially with hemophilia and thrombosis. Duke[4] has published some interesting observations on cases of purpura hemorrhagica which show that the coagulation time may be normal while the bleeding time is greatly prolonged. By the latter term he designates the time that a small wound will continue to bleed, as determined by pressing against it a bit of filter paper at definite intervals of time. He has connected the increased bleeding time in purpura with a marked deficiency in platelets, in consequence of which platelet thrombi fail to form in the wounded vessels. My work throws no light on this point, but it does demonstrate that severe purpura hemorrhagica may exist without any detectable abnormality in the factors concerned in the clotting of the blood. The tendency to bleeding in these cases cannot be referred apparently to a deficient power of coagulation.

Hemophilia.—I have had the opportunity of examining with care two cases of undoubted hereditary hemophilia and a third case of a young boy in which no history of inheritance could be obtained. The history of these cases is as follows:

REPORT OF CASES

CASES 1 and 2.—Joseph Y., aged 12 years, and Jesse Y., aged 8 years, sons of Joseph Y. of Baltimore, a Russian Jew. The hemophilic tendency in these children was inherited from the mother. She stated that three of her brothers died from hemorrhage; one at 17 years of age as the result of an operation on the tonsils; one at 6 years from a cut on the face made accidentally by a playmate, and one at the time of circumcision. She states also that a cousin, daughter of her father's brother, has married and has hemophilic boys. An effort to locate this latter family was not successful. In the present family of Joseph Y. there are seven children: three boys, Joseph, 12 years, Jesse, 8 years and Fred, 5 years, all markedly hemophilic, and four girls none of whom have exhibited any tendency to bleed. Great difficulty from bleeding has been experienced at various times with the three boys. All have suffered from serious hematomata due to accidents in playing. Joseph at the time of circumcision is said to have bled for a week. At 4 years of age he was brought to the Johns Hopkins Hospital with hemorrhage caused by biting the tongue while eating an apple. The hemorrhage, at first profuse, lasted nearly a week. It was partially controlled by cauterizing with lunar caustic. Parents gave a history of bleeding spells in the boy from slight injuries on four or five occasions. The coagulation time as then recorded was only six to twelve minutes. The method is not stated but probably the blood was taken by puncture through the skin and the result is therefore not reliable. He has been a patient at the hospital since this time on several occasions in connection with joint troubles. Fred when 3½ years of age was taken to the Hebrew Hospital, Baltimore, on account of a persistent hemorrhage from the tonsils supposed to be due to an accident. Bleeding continued for several days and was controlled finally or ceased finally after an injection of horse serum (8 c.c.)

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[3] Addis: Jour. Pathol. and Bacteriol., 1911, xv, 436.

[4] Duke: Jour. Am. Med. Assn., 1910, lv, 1185; Bull. Johns Hopkins Hosp., 1912, xxiii, 145.

In the experiments here reported only Joseph and Jesse were used as they were old enough to come to the laboratory and could be used conveniently for the operation of venepuncture.

Case 3.—A. H. S., 4 years old, patient in the Harriet Lane Home of the Johns Hopkins Hospital. Since his third month difficulty has been experienced with bleeding from small cuts, and injuries of any kind have been followed by "black and blue" areas in the region involved. At the time of admission to the hospital—March 25, 1913—the child was very anemic: red blood-cells, 1,730,000; white blood-cells, 15,300; Hb. 33 per cent.; platelets apparently normal, although no count was made. Large purpuric areas existed on right arm and leg, right shoulder, left tibia and right cheek. Right arm, hand and shoulder much swollen; right leg also swollen. The child remained in the hospital until May 1, 1913, and showed very marked improvement. A blood count made April 15, showed red blood-cells 4,270,000; white blood-cells 13,000 and Hb. 80 per cent. On three occasions human blood serum was injected subcutaneously; on April 12, 10 c.c.; April 14, 14 c.c., and April 24, 15 c.c. Through the kindness of Dr. John Howland I was given an opportunity to examine the blood on two occasions; once, the day after admission to the hospital and once just before his discharge. On each occasion the specimens of blood were obtained for me by Dr. W. L. Moss to whose kindness and skill I have been much indebted throughout this work.

COAGULATION TIME OF THE HEMOPHILIC BLOOD

The coagulation time was determined on specimens of 2 or 4 c.c. of blood obtained directly from the vein by means of the sterilized syringe and expelled at once into wide tubes (diameter 21 mm.), which had been cleaned carefully with a bichromate acid mixture. The clotting time was estimated up to the time that the clot was firm enough to allow the tube to be inverted. Comparisons were always made with specimens of blood taken from normal individuals by the same method. Tested by this method the time of clotting of normal blood varies usually between twenty and forty minutes. The time shown by the hemophilic blood at different periods was as follows:

Nov. 2, 1912..........	Joseph Y..............	Clot apparent in 3 hours, complete in 4 hours.
	Jesse Y................	Clot apparent in 3 hours, complete in 4 hours.

Dec. 21, 1912	Joseph Y.	Clot apparent in 4 hours, complete in 5 hours.
	Jesse Y.	Clot apparent in 4 hours, complete in 5 hours.
Jan. 18, 1913	Jesse Y.	Clot apparent in 3 hours, complete in 4 hours.
April 19, 1913	Joseph Y.	Clot apparent in 4 hours, complete in 5 hours.
	Jesse Y.	Clot apparent in 4 hours, complete in 5 hours.
April 28, 1913	Joseph Y.	Clotted between 2 and 2½ hours.[5]
May 17, 1913	Joseph Y.	Clotted in 3½ hours.
June 14, 1913	Joseph Y.	Clotted in 4 hours.
March 26, 1913	A. H. S.	Clotted between 2½ and 3 hours.
May 1, 1913	A. H. S.	Clotted between 3 and 4 hours.

It is apparent from these data that in the three cases examined there was a marked delay in the spontaneous coagulation of the hemophilic blood, such as has been reported by several other observers. So far as could be determined from the examinations made of the blood of the brothers Y., extending over a period of eight months, there was at no time an approach to normal, and in fact but little indication of any variation. The deficient coagulability was due to some permanent alteration in the properties of the blood. It is noteworthy in the case of A. H. S., that in spite of the fact that he had received during his stay in the hospital three injections of human serum and that his general condition had improved so greatly, the coagulation time, at the end, was as long or longer than when he first came into the hospital. In regard to the coagulation time of blood, it should be emphasized that errors may arise easily if the technic of obtaining the specimens fails in any respect. Constant and reliable results are obtained only in those cases in which the needle of the syringe enters the vein readily on the first puncture. When the vein is missed or transfixed and the lumen is found only after several trials, there is a likelihood that the specimen of blood may contain some tissue-juice, and therefore clot more rapidly than it would alone. This effect was shown very distinctly on one occasion with Jesse Y. On the first attempt the needle missed the vein, and only after several trials was it possible to draw about 2 c.c. of blood. When emptied into a tube this specimen clotted in ten minutes. A specimen of 8 c.c. was then obtained from the vein of the other arm. The technic was good, and a specimen of 2 c.c. placed in a tube clotted in the usual time, namely, between four and five hours.

No difficulty from hemorrhage was experienced in taking blood from the hemophilic patient, provided the vein was not wounded. On two occasions when the needle did not enter promptly, and there was probably some laceration of the vein, there developed later a somewhat extensive purpuric area which persisted for a long period.

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[5] In this case 1 c.c. only was taken for examination, and there is a probability that some tissue juice was mixed with this specimen, since difficulty was experienced in getting into the vein.

EFFECT OF THROMBOPLASTIC SUBSTANCE AND OF CALCIUM ON THE CLOTTING OF HEMOPHILIC BLOOD

As stated above, admixture with thromboplastic material of the tissues accelerates greatly the time of clotting. On several occasions this result was obtained with the active principle of the tissue extracts; that is to say, with the phosphatid (kephalin) extracted from brain tissue as described in a previous paper.[6] In one experiment the kephalin was dissolved in a 6 per cent. solution of dextrose and a control was made with a similar solution of dextrose without kephalin. The kephalin caused a marked acceleration in the clotting of both normal and hemophilic blood.

Normal blood: 1 c.c. blood plus 1 c.c. dextrose solution (6 per cent.) clotted in 10 minutes.
1 c.c. blood plus 1 c.c. of dextrose solution containing kephalin clotted in five minutes.

Hemophilic blood (Joseph Y.): 1 c.c. blood plus 1 c.c. dextrose solution clotted between two hours, ten minutes, and three hours, thirty minutes.
1 c.c. blood plus 1 c.c. dextrose solution containing kephalin clotted in ten to eleven minutes.

A similar result was obtained with specimens taken from Jesse Y.

In a second experiment the coagulation time of a mixture of blood with kephalin was compared with that of the undiluted blood. The specimens containing the kephalin were placed in narrow centrifugal tubes which would tend also to shorten the time.

Coagulation time of 2 c.c. blood: Normal, 30 minutes; Joseph Y., four to five hours; Jesse Y., four to five hours.

Coagulation time of 2 c.c. blood plus 1 c.c. dextrose solution containing kephalin: Normal, four to five minutes; Joseph Y., twelve minutes; Jesse Y., eleven minutes.

Similar results were obtained in a third experiment, in which the kephalin was added in aqueous solution, and in which consequently there was considerable hemolysis of the blood.

It is stated that the content in calcium of the hemophilic blood is normal (Nolf[7]), and that addition of calcium chlorid does not hasten the time of coagulation (Morawitz and Lossen[8]). In my experiments it was noted that the oxalated hemophilic blood gave a good deposit of calcium oxalate on centrifugalization, but the deposit to the eye seemed less than that obtained from similar specimens of normal blood. An attempt was made to determine the amount of calcium in small specimens of the blood (8 c.c.), but the results were unsatisfactory. In a single experiment it was found that addition of calcium chlorid to the hemophilic plasma hastened somewhat the time of coagulation, as follows:

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[6] Howell: Am. Jour. Physiol., 1912, xxxi, 1.

[7] Nolf: Eine neue Theorie der Blutgerinnung. Ergebn. d inn. Med., 1913, x, 275.

[8] Morawitz and Lossen: Deutsch. Arch. f. klin. Med., 1908, xciv, 110.

2 c.c. hemophilic plasma (Joseph Y.), coagulation time = four to five hours.

1 c.c. hemophilic plasma + 3 drops $CaCl_2$, ½ per cent., coagulation in two hours, thirty minutes.

1 c.c. hemophilic plasma + 6 drops $CaCl_2$, ½ per cent., coagulation in two hours, ten minutes.

ANTITHROMBIN IN HEMOPHILIC BLOOD

Examinations were made of the amount of antithrombin by the method previously described. In the case of the brothers Y., these examinations were made at irregular intervals during a period of several (eight) months, the blood being compared each time with a specimen of normal blood. In all cases the examination was made as soon as possible after taking the specimen from the vein, since experience had shown that when the blood is kept there is a gradual deterioration in the amount of antithrombin. The results of these comparisons are given in the accompanying table. It will be understood that the procedure was as previously described, that is to say, the clear plasma of the blood was heated to 60 C. and filtered. One drop of this heated plasma was then added to 2, 3, 4 and 5 drops of a thrombin solution, and, after an interval of fifteen minutes, ten drops of the fibrinogen solution (dried plasma) were placed in each tube. Owing to variations in the strengths of the thrombin solutions and fibrinogen solutions used, the different experiments are not comparable among themselves. In each experiment the antithrombin in the hemophilic plasma is to be compared with the normal blood taken at the same time and submitted to the same procedure.

Examination of these results shows that in general the amount of antithrombin in the hemophilic blood was somewhat greater than in the normal specimen with which it was compared. The excess, however, was not large and in some cases was not distinctly shown (experiments of December 21, April 19, April 28, May 17). Since in these latter cases the long coagulation time was still exhibited by the blood, it seems most probable that the characteristic delay in coagulation shown by hemophilic blood cannot be referred to an increase in the absolute amount of antithrombin present in the blood. As will be shown, however, in the next paragraph, there is good reason to believe that in these bloods there is always a relative excess of antithrombin, which is quite sufficient to account for the prolonged period of coagulation.

TABLE I.—Results of Examination for Antithrombin in Hemophilic Blood

Date	Name	Thrombin in Drops	Time of Coagulation
Oct. 19, 1912.....	Joseph Y. (hemophilic)	2	8 to 15 hours.
		3	45 to 50 minutes.
		4	20 minutes.
		5	15 minutes.
	John S. (normal)	2	2 to 8 hours.
		3	30 to 35 minutes.
		4	10 minutes.
		5	10 minutes.
Nov. 2, 1912.....	Joseph Y. (hemophilic)	2	4 to 18 hours.
		3	45 minutes.
		4	35 minutes.
		5	15 minutes.
	Jesse Y. (hemophilic)	2	45 minutes.
		3	20 minutes.
		4	15 minutes.
		5	10 minutes.
	W. H. H. (normal)	2	20 minutes.
		3	10 minutes.
		4	10 minutes.
		5	5 minutes.
Nov. 16. 1912.....	Joseph Y. (hemophilic)	2	6 to 15 hours.
		3	3 to 6 hours.
		4	30 minutes.
		5	20 minutes.
	Jesse Y. (hemophilic)	2	6 to 15 hours.
		3	3 to 6 hours.
		4	30 minutes.
		5	20 minutes.
	D. R. H. (normal)	2	3 to 6 hours.
		3	30 minutes.
		4	15 to 20 minutes.
		5	10 minutes.
Dec. 21, 1912.....	Joseph Y. (hemophilic)	2	No clot in 24 hours.
		3	Begun in 1 hour.
		4	20 minutes.
		5	10 minutes.
	Jesse Y. (hemophilic)	2	No clot in 24 hours.
		3	Begun in 2 hours.
		4	20 minutes.
		5	15 minutes.
	H., hospital patient (normal) ?	2	45 minutes.
		3	15 minutes.
		4	10 minutes.
		5	10 minutes.
	D. (normal)	2	No clot in 24 hours.
		3	?
		4	40 minutes.
		5	20 minutes.
Jan. 18, 1913.....	Joseph Y. (hemophilic)	2	No clot in 3 hours.
		3	15 minutes.
		4	10 minutes.
		5	5 minutes.
	Jesse Y. (hemophilic)	2	No clot in 3 hours.
		3	20 minutes.
		4	10 minutes.
		5	5 minutes.
	M. (normal)	2	1½ to 2 hours.
		3	10 minutes.
		4	5 minutes.
		5	5 minutes.

TABLE I.—RESULTS OF EXAMINATION FOR ANTITHROMBIN IN HEMOPHILIC BLOOD.—(Continued.)

Date	Name	Thrombin in Drops	Time of Coagulation
April 19, 1913....	Joseph Y. (hemophilic)	2	20 to 25 minutes.
		3	10 minutes.
		4	5 minutes.
		5	5 minutes.
	Jesse Y. (hemophilic)	2	20 to 25 minutes.
		3	10 minutes.
		4	5 minutes.
		5	5 minutes.
	John S. (normal)	2	15 to 20 minutes.
		3	10 minutes.
		4	5 minutes.
		5	5 minutes.
April 28, 1913....	Joseph Y. (hemophilic)	2	10 minutes.
		3	5 minutes.
		4	5 minutes.
		5	5 minutes.
	John S. (normal)	2	10 minutes.
		3	5 minutes.
		4	5 minutes.
		5	5 minutes.
May 17, 1913.....	Joseph Y. (hemophilic)	2	10 minutes.
		3	10 minutes.
		4	5 minutes.
		5	3 minutes.
	John S. (normal)	2	10 minutes.
		3	5 minutes.
		4	3 minutes.
		5	3 minutes.
March 26, 1913...	A. H. S. (hemophilic)	2	Small membrane at 25 minutes.
		3	10 minutes.
		4	5 minutes.
		5	5 minutes.
	John S. (normal)	2	Small membrane at 20 minutes.
		3	5 minutes.
		4	5 minutes.
			5 minutes.
May 1, 1913.....	A. H. S. (hemophilic)	2	?
		3	15 minutes.
		4	10 minutes.
		5	5 minutes.
	George S. (normal)	2	?
		3	5 minutes.
		4	5 minutes.
		5	5 minutes.

PROTHROMBIN IN HEMOPHILIC BLOOD

The relative amounts of prothrombin in the hemophilic and normal bloods were determined by the simple method, described above, of first oxalating the blood and then adding the optimum amount of calcium chlorid to the clear plasma. This procedure was carried out on a great many specimens of blood, normal and pathological. It may be said in general that the time of coagulation for normal human blood is quite constant, averaging about ten minutes, with variations from eight or nine to twelve or thirteen minutes. In normal dog's blood the time of coagulation is somewhat shorter, averaging about six minutes, with variations between five and nine or ten minutes. In the hemophilic bloods the results were entirely different, as shown by Table 2.

TABLE 2.—Results of Examination for Prothrombin in Hemophilic Blood

Date	Name	Calcium Chlorid, 0.5 Per Cent., in Drops	Time of Coagulation (5 Drops of Oxalated Plasma)
March 26, 1913...	A. H. S.	1	No clot.
	(hemophilic)	2	90 minutes.
		3	120 to 150 minutes.
		4	120 to 150 minutes.
	John S.	1	No clot.
	(normal)	2	9 minutes.
		3	12 minutes.
		4	14 minutes.
May 1, 1913......	A. H. S.	2	?
	(hemophilic)	3	Partly clotted in 3 hrs.
		4	Partly clotted in 3 hrs.
		5	?
	George S.	2	10 minutes.
	(normal)	3	14 minutes.
		4	20 minutes.
		5	30 minutes.
April 19, 1913....	Joseph Y.	2	No clot in 4 hours.
	(hemophilic)	3	No clot in 4 hours.
		4	No clot in 4 hours.
	Jesse Y.	2	Clot in 2 to 2½ hours.
	(hemophilic)	3	Clot in 2 to 2½ hours.
		4	Clot in 2½ hours.
	John S.	2	10 minutes.
	(normal)	3	12 minutes.
		4	18 minutes.
April 28, 1913....	Joseph Y.	2	Clot later than 5 hours.
	(hemophilic)	3	Clot in 5 hours.
		4	Clot later than 5 hours.
	John S.	2	11 minutes.
	(normal)	3	13 minutes.
		4	17 minutes.
May 17, 1913.....	Joseph Y. (hemophilic)	2	Clot in 3 hours to 3 hours, 10 minutes.
		3	Clot in 3 hours to 3 hours, 10 minutes.
		4	Clot later than 3½ hrs.
	John S.	2	8 minutes.
	(normal)	3	10 minutes.
		4	12 minutes.

As will be seen from examination of the table, the optimum amount of calcium in the normal was obtained with two drops of the solution of calcium chlorid. With this amount of calcium the clotting time of the normal plasma was, in the different experiments, 9, 10, 10, 11 and 8 minutes. The clotting time for the hemophilic bloods was 90, 180+, 240+, 120, 300, 180+ minutes.

The much delayed coagulation of hemophilic plasma under these conditions may be accounted for theoretically in several ways. It may be due, in the first place, to the presence of an excessive amount of antithrombin. The observations reported above give but little support to this explanation. The amount of antithrombin in hemophilic plasma may be somewhat greater than that found in normal blood, and according to my results, is never distinctly less than normal; but on the other hand, when it is present in normal amounts, the hemophilic blood still exhibits in a marked way the characteristic delay in coagulation when oxalated and again recalcified. In other words, there is no parallelism between the amount of antithrombin and the delay in coagulation, and we cannot therefore explain the latter phenomenon by reference to variations in the antithrombin. In the second place, the delayed coagulation of the hemophilic blood may be referred, as has been done by Sahli[9] and by Morawitz and Lossen, to a deficiency in thromboplastic substance, or rather to that particular form of thromboplastic substance which Morawitz has designated as thrombokinase. There is no satisfactory method of detecting variations in quantity of the thrombokinase. The authors named have arrived at the conclusion that thrombokinase is lacking in hemophilic blood (and hemophilic tissues), mainly by a process of exclusion of other possible explanations. I believe, and have given experimental reasons for the belief, that such a thing as thrombokinase does not exist. Morawitz's ingenious and attractive hypothesis in regard to this substance has proved to be an obstacle rather than an assistance in the study of the phenomenon of clotting. The reasons given for the existence of a kinase in the intestine with the property of activating trypsin, are convincing, since much in the way of direct proof is easily obtained. Any one may demonstrate that the mucous membrane of the intestine contains an organic substance which effects the rapid activation of trypsin. But no such proof is obtainable for the existence of a thrombokinase. From an experimental standpoint the whole matter is complicated here by the additional hypothesis that the kinase alone cannot activate thrombin, but requires the coactivity of calcium. That calcium is concerned in the activation of prothrombin to thrombin is beyond question, but every proof furnished to demonstrate that calcium alone is concerned in this activation is met by the objection that the kinase also is present in the solutions. Since this kinase has no known properties or reactions except that of assisting calcium in the activation of thrombin, the argument assumes the form of a perfect circle. Kinase is necessary to the formation of thrombin, hence if thrombin is formed a kinase is present. What is usually designated as a thrombokinase in the blood and other tissues is in reality the substance or substances which facilitate the process of clotting, and which have long been known under the terms zymoplastic or thromboplastic substances. According to my work, they consist essentially of a special phosphatid (kephalin?), which accelerates the process of clotting, not by any direct action on prothrombin, after the manner of a kinase, but by its neutralizing effect on the antithrombin. In the general sense of the term it is a thromboplastic substance, but not a thrombokinase. Whether or not this material is lacking in hemophilic plasma, I have not been able to determine in any wholly satisfactory way. Addis[3] reports certain experiments which he believes demonstrate that as regards this factor there is no difference between normal and hemophilic plasma, but his experiments do not seem to me to be conclusive. Sahli, on the other hand, reports experiments on the thromboplastic effect of washed blood corpuscles from normal and from hemophilic blood, which seem to show that the former contain more thromboplastic material than the latter. But this conclusion, if correct, is scarcely applicable to the case under discussion. The thromboplastic substance liberated in the blood after shedding comes, it is assumed usually, from the disintegration of the platelets. When blood is received at once into oxalate solutions, this disintegration is prevented. The platelets are fixed, indeed, permanently fixed. When the blood is centrifugalized they are thrown down unchanged, as may be shown by microscopic examination, and subsequent treatment with water or saline solutions shows that they now possess a rigidity altogether different from their original condition in the normal plasma. It is probable, therefore, that when the normal or hemophilic blood is oxalated immediately and centrifugalized, the clear plasma obtained has not received an accession of thromboplastic substance from disintegrating platelets. Nevertheless under these conditions, addition of calcium to such plasmas is followed by prompt and uniform clotting in the normal plasma and by a much delayed and variable clotting time in the hemophilic plasma. My own explanation of the cause of this difference is similar to that proposed by Addis, namely, that the trouble lies in a variation in the prothrombin. This view is discussed further in the succeeding paragraph. Outside of all theoretical considerations, it is well to emphasize the fact that the simple procedure described above, of oxalating plasma and then recalcifying by adding calcium chlorid, gives a convenient method of detecting hemophilic blood and of distinguishing it from the bloods of other hemorrhagic conditions.

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[9] Sahli: Deutsch. Archiv. f. klin. Med., 1910, xcix, 518.

THE CAUSE OF HEMOPHILIA

In the recent admirable monograph on hemophilia by Bulloch and Fildes,[10] the condition is defined as "an inherited tendency in males to bleed." The definition is unsatisfactory, in that it fails to suggest a cause for the condition, and possibly also in that it lays too much stress on the hereditary feature. There is no question, of course, that hemophilia is transmissible by heredity, and that most of the undoubted cases reported exhibit this history, but on the other hand it cannot be denied at present that cases may arise spontaneously. To exclude such cases from the group of hemophilia because there is no evidence of a similar condition in the family records, is not justifiable. In all probability such spontaneous cases may in turn be transmitted according to the law controlling this inheritance. Outside its transmissibility as a sex-limited inheritance, hemophilia is characterized clearly by certain reactions or properties of the blood which distinguish it from other hemorrhagic conditions in which there is also a "tendency to bleed." The main distinguishing feature of the hemophilic condition is the greatly delayed coagulation time of the blood, when the blood is removed from the vessels without coming in contact with the tissues. This peculiarity is demonstrated more easily and certainly, in contrast with other bloods, if the specimen of blood is first oxalated, then centrifugalized to obtain a clear plasma and then recalcified by the addition of a suitable amount of calcium chlorid. If the specimen so treated should show a coagulation time exceeding that of the normal blood (nine to twelve minutes), there would be reason for claiming the presence of a hemophilic condition, and the gravity of the condition would be in proportion to the length of time required for coagulation.

All recent workers agree on this delayed or deficient coagulability as the characteristic feature of hemophilia and attempts to explain the proximate or ultimate cause of the condition start from this point. The nature of the explanations offered varies of course with the theory of coagulation adopted. Morawitz and Lossen and Sahli, adopting the theory of coagulation proposed by Morawitz, have been led to believe that the defect of the hemophilic blood consists in a deficiency or lack of thrombokinase; Weil[11] has suggested that the delayed coagulation may be caused by the presence of some inhibiting body (antithrombin): Wright[12] has attributed the trouble, in part at least, to a deficiency in calcium; Nolf, in accordance with his special theory of coagulation, supposes that there is a quantitative or qualitative defect in the factor of coagulation designated by him as thrombozym. Addis in his series of thoughtful experiments has come to the conclusion that the essential difficulty lies in a change in the properties of the prothrombin. My own work has convinced me that the antithrombin theory of hemophilia is incorrect, in spite of the fact that my experiments were begun in the expectation of supporting this view. There is little or no positive evidence in favor of the view that a deficiency of calcium is the fundamental trouble, and I am persuaded that the explanations offered by Morawitz, Sahli and Nolf have been influenced by an incorrect theory of the process of clotting. Sahli's generalization that in the hemophilic there is a loss of thromboplastic power (thrombokinase), not only in the corpuscles of the blood, but in the tissues at large, is certainly not applicable in all cases. The slow clotting hemophilic blood may coagulate quite promptly if it is brought into contact with the tissue juices of the external tissues. There are at present, so it seems to me, no positive facts supporting this general view of a defect in thromboplastic material in the hemophilic blood. My own experiments have led me to believe that the trouble lies, where it was traced by Addis, in the factor of prothrombin; that is to say, the material from which the thrombin is formed. The experiments described above on the coagulation time of oxalated blood after the addition of calcium can only mean that this prothrombin material is deficient in quantity or altered in character. Addis has adopted the latter view. He believes that the prothrombin of the hemophilic blood is present in normal amounts, but is so altered in properties as to require a longer time than normal for activation to thrombin. This explanation has seemed to me to be improbable, because, in the first place, I have found, as reported in this paper, that addition of thromboplastic (phosphatid) material accelerates greatly the time of clotting of the hemophilic blood. Addis admits this fact, but claims that it is true only when large amounts of this material are used. Assuming that this latter qualification is correct, it does not affect the main conclusion that the prothrombin possesses its normal properties in relation to activation by calcium, since the thromboplastic material is effective only by virtue of the fact that it removes the antagonistic influence of the antithrombin. However, the point that Addis raises can be settled only by isolating the prothrombin from the hemophilic plasma and testing the action of calcium on it in comparison with prothrombin obtained by the same method from normal blood.

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[10] Bulloch and Fildes: Hemophilia, Eugenic Laboratory Memoirs. University of London. 1911. xii.

[11] Weil: Presse méd., 1905, p. 672; Bull. et mem. Soc. méd. d. hôp. de Paris. Oct. 26, 1906.

[12] Wright: Brit. Med. Jour., 1893, p. 223.

I have been able, fortunately, to obtain the prothrombin from blood plasma by the simple method which I have employed already for the isolation of thrombin. The method is as follows: Blood is obtained from a vein of the arm by means of a syringe and is oxalated at once (8 c.c. of blood to 1 c.c. of a 1 per cent. solution of sodium oxalate made up in sodium chlorid solution 0.9 per cent.). The specimen is centrifugalized and the clear plasma is drawn off. To this plasma is added an equal volume of acetone and the precipitate is filtered off through a small filter. The filter paper is opened, the precipitate is spread to a thin layer and is then dried rapidly in a current of air from an electric fan. The dried filter paper with its adherent precipitate is cut into small pieces and is covered with water (8 or 10 c.c.) and allowed to stand for about half an hour. The extract is then filtered. The opalescent solution contains prothrombin, as can be shown most satisfactorily by its reaction with fibrinogen solutions. The fibrinogen solutions used for this purpose I have prepared from the plasma of cat's blood by a modification[13] of Hammarsten's method of repeated precipitation by half saturation with sodium chlorid. If the fibrinogen is precipitated three times the final solution in 0.9 per cent. sodium chlorid (with a trace of sodium bicarbonate if necessary) gives no coagulation at all on the addition of calcium, but clots readily with thrombin. With such solutions of fibrinogen, or indeed with the less pure solutions obtained by one or two precipitations, the presence of prothrombin in the solutions described above may be demonstrated very readily by experiments, of which the following is an example:

1. Fibrinogen solution, 10 drops + $CaCl_2$, ½ per cent., 1 drop = no clot in twenty-four hours.
2. Fibrinogen solution, 10 drops + prothrombin solution 3 drops = no clot in twenty-four hours.
3. Fibrinogen solution 10 drops + prothrombin solution 3 drops + $CaCl_2$, ½ per cent., 1 drop = clot in 2 to 3 minutes.

It should be stated that fibrinogen solutions prepared as described are not constant in their reactions. In some cases they clot very readily with thrombin; in other cases the clotting requires a longer time, and on standing for twenty-four hours or more the fibrinogen may undergo a modification of some kind so that it loses the property of yielding a clot on the addition of thrombin. In all cases, however, the freshly prepared fibrinogen may be used to demonstrate the presence of the prothrombin, since the solutions of the latter have no effect on the fibrinogen until calcium is added, and then the thrombic action is clearly shown. In order to determine whether or not the prothrombin from the hemophilic blood differs in its reaction to calcium from that of normal blood, I have prepared the prothrombin from one of the hemophilic subjects used in this investigation (Joseph Y.) and compared it with the prothrombin from a normal blood. The following results were obtained:

Experiment, Oct. 19, 1913.—Eight cubic centimeters of blood taken from Joseph Y. and 8 c.c. from a normal (John S.). Each specimen was oxalated and treated with acetone as described above. The aqueous solutions of prothrombin were tested on a freshly prepared fibrinogen solution.

Control Experiments.—Fibrinogen solution, 10 drops + water 5 drops + $CaCl_2$ (½ per cent.) 1 drop = no clot in twenty-four hours.

Fibrinogen solution, 10 drops + prothrombin solution 5 drops = no clot in twenty-four hours.

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[13] Howell: Am. Jour. Physiol., 1910, xxvi, 461.

Prothrombin from Normal Blood.—Fibrinogen solution 10 drops + prothrombin solution 5 drops + $CaCl_2$, 1 drop = clot in twenty-eight minutes.

Fibrinogen solution 10 drops + prothrombin 3 drops + $CaCl_2$, 1 drop = clot in 50 to 60 minutes.

Prothrombin from Hemophilic Blood.—Fibrinogen solution 10 drops + prothrombin solution 5 drops + $CaCl_2$, 1 drop = clot in twenty minutes.

Fibrinogen solution 10 drops + prothrombin solution 3 drops + $CaCl_2$, 1 drop = clot in fifty minutes.

This experiment, which was repeated several times with similar results, demonstrates quite definitely that the separated prothrombin from hemophilic blood yields active thrombin in the presence of calcium quite as readily as the prothrombin from normal blood. The qualitative difference claimed by Addis does not exist. In explaining the delayed coagulation of the hemophilic blood we must assume, it seems to me, that the prothrombin is present in subnormal amount in the circulating blood. Since the antithrombin, on the contrary, exists in normal or even in sligthly supranormal amounts, the delay in coagulation of the shed blood is readily explained. On the basis of the facts presented in this paper, I would conclude that the essential condition in hemophilic blood which is immediately responsible for its delayed coagulation is a subnormal amount of prothrombin in the circulating blood.

Hemophilia may be defined as a condition, limited to the male, in which the coagulation time of the blood is markedly prolonged in consequence of a deficiency in the amount of the contained prothrombin, with the additional characteristic that the defect is transmissible by heredity in accordance with the so-called law of Nasse.

The ultimate cause of this condition cannot be stated. So far as we know, the prothrombin present in blood-plasma is furnished by the blood-platelets, and it is reasonable to assume that the defect in question is referable to some functional change in these elements.

THROMBOSIS

During the course of this work the opportunity has offered to examine several cases of thrombosis in which there were no obvious mechanical or inflammatory conditions to account for the trouble. The cases are few in number, and unfortunately the examination was not complete in each case, but the results seem to be suggestive.

CASE 4.—Dr. H., just recovering from mild attack of thrombosis involving the saphenous and the abdominal veins. Some soreness and edema over region involved. He had had several similar attacks at intervals of some weeks. Specimen of 8 c.c. of blood taken from an arm vein and compared with similar specimen from a laboratory attendant (John S.).

The results of this test indicate that the blood of the thrombotic patient contained less antithrombin than the normal with which it was compared, and, indeed, less than any of the normals used in any of these experiments.

Coagulation time (4 c.c.): Patient, 29 to 30 minutes.
Normal, 38 to 39 minutes.

ANTITHROMBIN TEST

Heated Plasma Drops	Thrombin Drops	Time Interval Minutes	Fibr. Sol. Drops	Coagulation Minutes
		Normal.		
1	2	15	10	40
1	3	15	10	10
1	4	15	10	5
1	5	15	10	5
		Patient.		
1	2	15	. 10	10
1	3	15	10	5
1	4	15	10	5
1	5	15	10	5

CASE 5.—Charles G., patient in the Johns Hospkins Hospital, service of Dr. Barker. Aged 52. Onset of attack one month previous to admission; dyspnea on exertion, pain in left side, swelling of feet. Physical findings: dyspnea, hydrothorax, mitral and aortic insufficiency. Blood-pressure. 140. Blood-count, r. b. c., 4,300,000; w. b. c., 7,400; Hb., 90 per cent. The day before the blood was examined the patient developed a marked swelling of the whole left leg, diagnosed as due to thrombus in the left femoral or iliac vein. Some of the superficial veins at left elbow firmly thrombosed.

Specimen of blood, 10 c.c., taken from arm vein and compared with a similar specimen from one of the laboratory attendants (M.).

Coagulation time (2 c.c.): Patient, 8 minutes.
Normal, 41 minutes.

ANTITHROMBIN TEST

Heated Plasma Drops	Thrombin Drops	Time Interval Minutes	Fibr. Sol. Drops	Coagulation Minutes
		Normal		
1	2	15	10	*
1	3	15	10	10†
1	4	15	10	5
1	5	15	10	5
		Patient.		
1	2	15	10	5
1	2	15	10	2
1	2	15	10	2
1	2	15	10	2

* First membrane at twenty minutes.
† Partial.

In this case also the amount of antithrombin was distinctly less than in the normal. In fact the clotting with the thrombotic plasma was so rapid as to indicate the practical absence of antithrombin in its heated plasma.

PROTHROMBIN TEST

Oxalated Plasma Drops	$CaCl_2$, ½ Per Cent. Drops	Coagulation Minutes
	Patient.	
5	2	7
5	3	7
5	4	9
5	5	11
	Normal.	
5	2	10
5	3	14
5	4	17
5	5	19

The more rapid clotting of the oxalated plasma of the thrombotic blood may have been due to a greater amount of prothrombin or to a diminished amount of antithrombin. The previous test for antithrombin indicates that the latter explanation is probably the correct one, and this conclusion is borne out by a subsequent experiment in which the serum from the patient and from the normal were compared in regard to their strength in thrombin, the precaution being taken of adding to each an equal volume of kephalin-solution to neutralize the antithrombin present. This test gave the following result:

COMPARISON OF STRENGTH IN THROMBIN

Fibrinogen Solution Drops	Serum and Kephalin Drops	Coagulation Minutes
	Patient.	
10	2	12
10	3	6
10	4	5
10	5	3
	Normal.	
10	2	10
10	3	5
10	4	5
10	5	3

According to this test there was practically no difference in the amount of thrombin in the two specimens of serum.

CASE 6.—Mrs. N., private patient of Dr. Thayer. History of two attacks of thrombosis — one six years previously with evidence of thrombosed veins in calf, groin and inner side of leg, one beginning four months before examination and following attack of measles. There were pain and tenderness over left femoral vein, knots in groin and under skin of legs, first on left side, later on right side. In bed for three months. On one occasion when convalescing there was a sudden attack of severe pain in side, with marked dyspnea. A similar attack followed after an interval of some time. Examination of the blood was made four months after beginning of last attack when the patient had recovered and showed no physical signs except slight edema in legs.

Coagulation time (2 c.c.): Mrs. N., 20 to 22 minutes.
Normal: Dr. D., 40 to 43 minutes.

PROTHROMBIN TEST

Five drops plasma + 2 drops $CaCl_2$ (½ per cent.) = clot in nine minutes.
Five drops plasma + 3 drops $CaCl_2$ (½ per cent.) = clot in twelve minutes.

ANTITHROMBIN TEST

This test was made with three dilutions of a new stock of thrombin. In two of these the concentration was too great, so that the tubes clotted more rapidly than was convenient for a decisive comparison. In each case, however, the clotting in the tubes containing the heated plasma from the patient preceded that in the controls, indicating, therefore, less antithrombin in the patient's blood. This difference was shown most distinctly with the third dilution of thrombin used as follows:

Heated Plasma Drops	Thrombin Drops	Time Interval Minutes	Fibrinogen Drops	Coagulation Minutes
		Normal.		
1	3	15	10	15 to 20
		Patient.		
1	4	15	10	15 to 20
1	3	15	10	7
1	4	15	10	5

CASE 7.—In a fourth case of thrombosis examined the results were negative. This patient was a hospital nurse with a history of repeated attacks, diagnosed by Dr. Boggs as due to venous thrombosis. At the time of examination of her blood she had been free from any trouble for several months. The examination made was incomplete, including only the coagulation time, thirty-five minutes, and the prothrombin test, ten minutes. As these times were entirely normal the antithrombin tests were not made, owing to circumstances which could not be controlled. This examination was made May 31. Later in the summer the patient had another severe attack, but was not accessible for examination.

The number of cases reported is small, but the indications from the blood examinations of a diminution in antithrombin, especially in Case 2, are sufficiently positive to warrant a suspicion that herein may lie the important factor responsible for the formation of a thrombus. If the antithrombin constitutes a normal defensive agency against intravascular clotting, a diminution in this substance will bring about a condition in which spontaneous coagulation will be favored, particularly in those parts of the circulation in which the mechanical conditions are such as may lead to a partial stasis of the circulation.

In the hemophilic blood there seems to be a relative excess of antithrombin, owing mainly to an actual diminution in the amount of prothrombin. In the blood of patients showing spontaneous thrombosis, just the opposite condition prevails of a deficiency in antithrombin relative to the amount of prothrombin present.

SUMMARY

1. Methods are described for testing the relative amount of prothrombin and antithrombin in the blood.

2. The application of these methods to hemophilia shows that the blood in this condition is deficient in prothrombin. The antithrombin may be normal or somewhat greater than normal. The characteristic peculiarity of hemophilic blood is its markedly delayed time of coagulation. This peculiarity is explained by the diminution in amount of the prothrombin which results in a relative excess of antithrombin.

3. The detection of a hemophilic condition of the blood is facilitated by first oxalating the blood and then recalcifying with an optimum amount of calcium. Under these conditions the time of clotting exhibited by normal plasma is very constant (nine to twelve minutes). That of hemophilic blood is greatly delayed.

4. In patients suffering from spontaneous thrombosis of the veins there is evidence of a diminution in the antithrombin of the blood, the prothrombin being normal. It is suggested that this deficiency in antithrombin operates as a favoring, perhaps as a determining, factor in the production of the thrombus.

5. In purpura hemorrhagica and other forms of so-called purpura, no evidence was found of any variation from normal in either the antithrombin or the prothrombin.

A CLINICAL STUDY OF AMYLASE * IN THE URINE

WITH ESPECIAL REFERENCE TO THE PHENOLSULPHONEPHTHALEIN TEST†

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Since Majendie,[1] in 1846, first found an amylolytic enzyme in human blood, and later, in 1863, Cohnheim[2] wrote of its presence in the urine, Plósz and Tiegil,[3] Foster,[4] Lépine[5] and many other writers have confirmed these earlier investigators and attempted to determine the quantitative value of amylase with reference to certain pathological conditions, more particularly those of the kidney. All the various methods devised were unwieldy and inaccurate however, and most of the information gained contradictory. In 1908 Wohlgemuth[6] devised a quantitative test which for the simplicity, accuracy and uniformity of its results so far surpassed any test previously proposed that it has been generally adopted by chemists and clinicians alike for the estimation of amylase in blood, urine, feces and other body substances.

Nearly all the contributions to our literature on this subject have come from French and German writers, and in Germany particular attention has been directed to the quantitative estimation of amylase in blood and urine.

Wohlgemuth's original method devised for the quantitative estimation of amylase has been followed by numerous investigations into the experimental and clinical aspects of this ferment as found in the body fluids. The largest portion of this work has been done by Wohlgemuth and his pupils and has yielded very interesting results.

In order that we may have a clearer understanding of what is to follow, it seems advisable to give in detail the technic of Wohlgemuth's

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* Throughout this paper the term amylase has been used in preference to the term diastase so generally employed by German writers, amylase having a more restricted significance than diastase; "d" as a means of expressing the readings obtained is used simply in deference to the terminology employed in Wohlgemuth's original method.

† From the Blumenthal Fellowship Foundation of the Medical Clinic, College of Physicians and Surgeons, Columbia University.

†Submitted for publication, Aug. 1, 1913.

1. Wajendie: Compt. rend., Acad. d. sc., 1846, xxiii, 189.
2. Cohnheim: Virchow's Arch. f. path. anat., 1863, xxviii. 241.
3. Plósz and Tiegil: Arch. f. d. ges. Physiol. (Pflügers), 1873. vii, 391.
4. Foster, M.: Jour. Anat. and Physiol., 1867, i. 107.
5. Lépine: Compt. rend., Acad. d. sc., 1891, cxiii, 1014.
6. Wohlgemuth. J.: Biochem. Ztschr., 1908, ix, 1.

"starch-iodin" method for the quantitative estimation of amylase as outlined in his most recent publication on this subject.[7] This differs in a few details only from his original method, which may be found in any text-book on physiological chemistry.

TECHNIC

Ten test-tubes numbered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 are placed in a test-tube stand (these tubes must be thoroughly cleansed, rinsed in distilled water and carefully dried). To each tube is added 1 c.c. of a normal saline solution from a graduated pipet (except in Tube 1, which contains 1 c.c. of the fluid to be tested). With a 1 c.c. pipet, accurately graduated into 0.1 c.c., draw up 1 c.c. of fluid to be tested and add to Tube 2, thoroughly mixing the fluids by three times drawing up the mixture of normal saline solution and test fluid and again expelling contents into the tube. Then finally draw up 1 c.c. of the fluid now diluted 1 to 2 and place this in Tube 3, repeating the same process of mixing and again withdrawing 1 c.c. of mixture. This is to be repeated in all the succeeding tubes and in the last tube the 1 c.c. withdrawn can be discarded. This will give the following amounts of fluid to be tested in each tube (seven tubes suffice in most cases).

No. 1 = 1.0 c.c.; No. 2 = 0.5 c.c.; No. 3 = 0.25 c.c.; No. 4 = 0.125 c.c.; No. 5 = 0.0625 c.c.; No. 6 = 0.032 c.c.; No. 7 = 0.016 c.c.; No. 8 = 0.008 c.c.; No. 9 = 0.004 c.c.; No. 10 = 0.002 c.c.

Now to each tube are added 2 c.c. of 0.1 per cent. starch solution (Kahlbaum's soluble starch), the tubes fitted into a wire cage after shaking gently, the cage placed on a water-bath at 38 C. for half an hour. The temperature should be very carefully watched, should be kept within one-half degree of 38 C. and the time accurately measured. At the end of this time all tubes are withdrawn and placed in ice-water for five minutes to inhibit further amylolytic activity and are then replaced in test-tube stand. To each tube is then added 2 drops of fiftieth-normal iodin solution which must be freshly prepared from a stock solution of tenth-normal strength daily.[8] One-to-one-thousand starch solution should be freshly prepared every three days and kept in refrigerator.

READING

If the urine is normal the first two or three tubes will be golden yellow in color, all starch having been digested, while the fourth will be reddish with no tinge of blue, the fifth violet and the others blue.[9] The tube from which the reading is taken is the deep-red tube; this tube shows that all starch has been digested at least to the dextrin stage.

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[7] Wohlegmuth, J., and Noguchi, Y.: Berl. klin. Wchnschr., 1912, xxiii, 1069.

[8] In case 2 drops of iodin solution to each tube is not sufficient to bring out a permanent color, add as many more drops to the tube as will be necessary, being careful to add exactly the same number of drops to each of the other tubes.

[9] The various gradations in color as given above are not always the same: in fact it may be difficult to determine in some instances which tube constitutes the end-point or reaction tube but after some practice, the eye becomes trained to recognize that tube which no longer contains a bluish tint. Corbett (Quart. Jour. Med., 1913, vi, 351) in a very recent publication emphasizes the "mauve tube" as the "limit" tube and calculates from the tube preceding this, (the one with a "reddish-yellow color.") Wohlgemuth (see Note 7) defines the end point as follows: "Dasjenige Gläschen, in welchem der erste blaue Farbenton auftritt, das also bei Zusatz von Jod rotblau wird, gilt als Grenze (Limes) der Wiksamkeit und aus der in dem vorhergehenden Gläschen enthaltenen Serummerge wird die Fermentstärke berechnet."

The calculation is then made as follows: In Tube 4 there was 0.125 c.c. urine or fluid which digested 2 c.c. of a 0.1 per cent. starch solution in half an hour at 38 C. Therefore 1 c.c. of fluid to be tested would digest starch according to the following equation:

$$0.125 : 2 \text{ c.c. (starch)} : : 1 \text{ c.c.} : X = 16$$

One c.c. of fluid digested 16 c.c. of a 0.1 per cent. starch solution in half an hour; this Wohlgemuth designates as follows:

$$d\frac{38^\circ}{30'} = 16$$

When twenty-four-hour digestion is employed he expresses it:

$$D\frac{38^\circ}{24 \text{ hr.}} = X.$$

The present work was undertaken with the object of determining two things: first, the clinical value of the estimation of amylase in the urine in determining the functionating powers of the kidney in various diseases, more particularly in renal and cardiac cases; second, the relationship between this test and another test of renal function, namely, the phenolsulphonephthalein test of Rowntree and Geraghty.

Most of the cases here reported fall under renal or cardiac headings, as these two conditions are the ones in which functional tests are most often made. But several other diseases have also been investigated with very interesting results. I had hoped also to make comparisons of the amylolytic value of the blood-serum synchronously with that of the urine, but, except in a few cases, this has not been possible, and will have to be taken up at some future date. In all cases investigated, samples of a twenty-four-hour specimen were used for reasons which will be explained later.[10]

The quantitative estimation of amylase in the urine as a test for the functional activity of the kidneys has been advanced by Wohlgemuth,[11] Benczur,[12] Wynhausen,[13] Rosenthal,[14] Marino,[15] Corbett[8] and Neuman.[16] Wohlgemuth[11] used it in conjunction with phloridzin, indigo-carmin and cryoscopy tests to determine unilateral disease of the kidney and found in a series of some fifty cases that it, with the freezing-point test, gave the most valuable results in estimating the relative functionating powers of the two kidneys. Wohlgemuth,[7] Corbett,[8] Neuman[16] and Rosenthal[14] have shown that the amount of amylase in the urine of normal individuals varied within very narrow limits, and for a given individual was almost constant, provided a twenty-four specimen was used. That there may be great variations in the amylolytic power of individual specimens of urine passed at certain times during the twenty-four hours, Wohlgemuth has shown as follows:[17] 1. There is more amylase in urine of fasting periods, that is, just before meals. 2. The amount begins to diminish after meals and gradually sinks until three or four hours after a meal, then gradually begins to rise again. This confirms the earlier investigations of Grützner,[18] Gehrig,[19] Hoffman,[20] Rosenberg[21] and Leo,[22] who worked with cruder methods.

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[10] A few cubic centimeters of toluol should be added to all twenty-four-hour specimens, to prevent bacterial growth. This does not interfere with the "d" readings, and preserves the urine for six months or more, giving the same "d" reading at the end of that time as when freshly voided.

[11] Wohlgemuth, J.: Ztschr. f. Urol., 1911, i, 801.

[12] Benczur, J.: Wien. klin. Wchnschr., 1910, xxiv, 890.

[13] Wynhausen, O. J.: Berl. klin. Wchnschr., 1910, xlvi, 2107.

[14] Rosenthal, A.: Deutsch. med. Wchnschr., 1911, xxxvii, 923.

[15] Marino, E.: Deutsch. Arch. f. klin. Med., 1911, ciii, 325.

[16] Neuman: Deutsch. Arch. f. klin. Med., 1913, cix, 164.

It has also been shown by Wohlgemuth[23] by experiments on dogs that neither the kind nor amount of food taken has any effect on the quantity of amylase in the blood-serum. Schlesinger[24] found the same for man, while Corbett[8] concludes that in human beings the quantity of amylase in the twenty-four-hour urine does not vary even with marked dietary changes. He gives one instance, however, that of an infant aged 9 months, who had never had unaltered starch food before, and whose urine, after three days' administration of starch-containing food, showed an increase in amylolytic power amounting to almost five times as much as before the giving of starch. Neuman[16] also concludes that changes in diet have no effect on the quantity of amylase in urine.

The influence[17] of sex on the amount of amylase in the urine shows that the urine of males has a slightly higher "d" reading than that of females. This, however, is so small as to be negligible in clinical work.

According to Wohlgemuth,[17] Corbett,[8] Wynhauser[13] and Marino,[15] the reaction and salt concentration of the urine has no appreciable effect on the "d" readings. In this connection it may be mentioned that Cole,[25] working with a pure (dialyzed) solution of ptyalin, shows that the effect of any electrolyte on the rate of action of the ferment is dependent on two factors — first, the acceleration due to anions other than hydroxylions, and second, the depression due to kations and hydroxylions.

Wohlgemuth[26] himself, after careful studies of the salivary amylase, pancreatic amylase and the amylase of blood-serum, all of which he found to have the same properties, came to the following conclusions:

1. Sodium chlorid increases amylolytic action in twenty-four hours' digestion ten fold.

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17. Wohlgemuth: Biochem. Ztschr., 1909, xxi, 432.
18. Grüttzner: Breslauer ärztl. Ztschr., 1882, xvii, 193.
19. Gehrig, J.: Arch. f. d. ges. Physiol. (Pflügers), 1885, xxxviii, 38.
20. Hoffman: Arch. f. d. ges. Physiol. (Pflügers), 1887, xli, 148.
21. Rosenberg: Dissertation, Tübingen, 1890.
22. Leo: Verhandl. d. VII. Kongr. f. inn. Med., 1888, 364.
23. Wohlgemuth, J.: Biochem. Ztschr., 1909, xxi, 381.
24. Schlesinger, W.: Deutsch. med. Wchnschr., 1908, xiv, 593.
25. Cole: Jour. Physiol., 1904, xxx, 202.
26. Wohlgemuth, J.: Biochem. Ztschr., 1908, ix, 10.

2. The lowest dilution in which sodium chlorid seemed to have an accelerating action was 0.002 to 0.00097 per cent.

3. The increased effect of sodium chlorid is due to the anion chlorid. therefore all other chlorid-containing neutral salts accelerate the enzyme.

4. Of the other halogen ions bromin also increases the action; also iodin, but to a less degree, while fluorin inhibits.

5. Alkalies, except sodium carbonate, inhibit the action of amylase and destroy it by prolonged action.

6. Neutral salts like sodium phosphate, oxalate and acetate inhibit the action of amylase, whereas the nitrate, nitrite and chlorate increase the action. Sodium sulphate is indifferent.

7. Alanin and leucin inhibit, glycocol is indifferent.

8. Colloid metals (gold, silver, copper and iron), inhibit in proportionately smaller concentration, while in strong dilution they are indifferent and the addition of sodium chlorid does not alter their behavior.

As the amylase in urine is probably derived directly from that of the blood it must have the same properties as that of the blood. It can, therefore, readily be seen how difficult it would be to determine the individual factors concerned in the composite action of the various ions on the amylolytic power in such an ion complex as the urine. Of the urines I have studied, some two hundred in number, I have had only two, and both were from the same patient, which showed an alakine reaction; all the others were neutral or acid, the majority being acid. No appreciable effect on the "d" readings caused by reaction could be noted, except when decomposition was evident, this seeming to accelerate the action of amylase.

Other factors affecting action of the ferment in urine must here be mentioned. First, the action of blood. It has been shown[27, 28] that blood and various organ extracts have a marked accelerating action on the amylolytic activity of pancreatic juice, saliva, etc. So that urine containing blood will show a much higher amylolytic power than normal urine. Dudley Corbett,[8] in a very recent publication has also demonstrated that the influence of blood on the amylolytic action of the urine is a strongly accelerating one. Neuman,[16] however, states that in "several cases" during menstruation no effect could be noted. He does not state definitely, however, how much blood was present nor does he say whether the specimens examined were complete twenty-four-hour ones. Both these factors are important, particularly the former, as I have often centrifuged specimens of urine from menstruating women and in the sediment found only small numbers of red blood-cells, absolutely no macroscopic evidence of blood being present. It is only reasonable to

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[27] Wohlgemuth, J.: Biochem. Ztschr., 1911, xxxiii, 303.

[28] Pozerski, L.: Thèse de Paris, 1902, 70.

suppose that in these cases when such relatively minute quantities of blood were present, no, or very slight, alteration in the "d" value would be found.

Another factor which must be considered in regard to its effect on amylolytic activity in the urine is albumin. Very few authors have dealt with this at all. Lüthje[29] found high amylase value in albuminous urines. Rosenthal[14] found that the chronic interstitial forms of nephritis showed uniformly lower readings that did other forms, and generally less albumin is found in the chronic interstitial forms. He draws no deductions, however. Benczur concludes that high "d" readings are sometimes found in nephritics and other albuminuric conditions. He argues that his and Wohlgemuth's experiments[30] in which they found increased "d" value for blood-free kidney extracts of diabetic animals, show that the kidney plays some part in the production of urinary amylase, and further, that the inflammatory condition which produces albuminuria may also serve to stimulate the kidney cells to increased amylase production. Neuman[16] denies any influence on the part of albumin or pus. Corbett, whose series of cases is small, gives this subject more detailed attention and theorizes as follows: The damage of kidney structure may be equally severe in cases with little or much albumin. The presence of much albumin is attributed to increased permeability of the kidney and the high "d" values so often obtained in these cases are due to the same factor. "For," he argues, "if the renal cells are permeable to the complex protein mixture, generally termed albumin, they should the more readily allow the passage of a simpler colloid, such as amylase." To support this theory he refers to cases of eclampsia with much albumin and many casts in which the "d" values were very high and in which there must have been severe damage to kidney structure. All the clinical evidence to date certainly points to higher "d" values in those forms of nephritis with high albumin content of the urine than in those forms with little or no albumin which almost invariably give low readings for "d."

In stating the results in my own series of cases I have adopted a purely arbitrary method in comparing the amounts of albumin found in different cases; for instance, anything tabulated as trace or faint trace is designated as "little albumin," while anything from heavy trace to much albumin or a definite quantitative figure is designated as "much albumin."

On examination of the figures in Table 1 with reference to the influence of albumin on the "d" reading, thirty-four cases[31] are found which have varying degrees of albuminuria; twelve cases which have

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[29] Lüthje, H.: Festschr. f. J. Rosenthal, 1906, ii, 131-138.

[30] Wohlgemuth, J., and Benczur: Biochem. Ztschr., 1909, xxi, 460.

[31] Case 29 is omitted as here the pus was very large in amount and was probably the main source of the albumin.

Case	Name	Sex	Date	Amylase	Urine				
					Quant. c.c.	Sp. Gr.	Albumin	Casts	Blood
1	D. W.	M.	10/31/12	8	1,770	1,008	Tr.	Many hyal. and gran.	Occ. R. B. C.
			1/15/13	2	1,200	1,015	H. Tr.		
			3/ 6/13	4	2,020	1.020			
			3/13/13	4	1,500	1.009			
			3/22/13	8	1.200	1.015	H. Tr.		
2	L. K.	F.	10/31/12	4	850	1.020	H. Tr.	Many hyal. and gran.	0
3	E. H.	F.	10/31/12	2	1.230	1.012	V. F. Tr.	Few	0
4	A. P.	F.	10/31/12	8	900	1.018	Much	Waxy gran., hyal.	Few R. B. C.
5	J. K.	M.	11/ 3/12	2	1,830	1.027	F. Tr.	Hyal., gran.	Few R. B. C.
6	M. R.	M.	11/ 3/12	4	1,500	1.020	V. H. Tr.	Gran., waxy hyal.	Few R. B. C.
7	A. W.	M.	11/27/12	2	1,620	1,008	F. Tr.	Hyal., gran.	0
			12/20/12	0	1,740	1.006			
			2/ 1/13	2	1.560	1.010			
8	G. D.	M.	11/ 2/12	0	930	1.019	V. F. Tr.	Hyal., gran. (many)	Few R. B. C. once.
			12/16/12	16	1,830	1.013			
			5/11/13	2	2,040	1.012			
9	S. D.	F.	12/22/12	4	1,400	1.012	F. Tr.	Occ. hyal., gran.	Few R. B. C.
			1/ 9/13	4	1,300	.....			
			2/ 1/13	4	1,365	.....			
10	M. R.	M.	1/10/13	2	2,075	.....	V. F. Tr.	0	0
			1/22/13	4	790	1.020			
			2/ 3/13	2	790	1.030			
			2/14/13	4	1,230	.....			
11	J. S.	F.	1/10/13	4	1,100	.....	V. F. Tr.	0	Occ. R. B. C.
			1/16/13	0	1,630	1.012			
			1/23/13	4	1.280	.....			
			1/26/13	4	730	1.016			
			1/28/13	4	1.450	.....			
12	G. H.	M.	1/15/13	32	1,050	.....	H. Tr.	Gran., hyal.	0
13	F. R.	M.	1/18/13	2	1.200	.....	H. Tr.	Gran., hyal.	0
			2/26/13	2	1.760	.....	F. Tr.		
14	R. P.	F.	1/18/13	4	1,800	.....	V. F. Tr. (Sugar)	0	R. B. C. few.
15	C. M.	M.	1/26/13	2	2,700	.....	H. Tr.	Many hyal., gran.	Many R. B. C.
			1/31/13	2	2,400	.....			
			2/14/13	2	1,400	.....			
16	M. S.	F.	2/ 3/13	8	2,705	1,036	H. Tr.	Hyal., gran.	0
17	J. T.	M.	1/21/13	2	630	.....	V. H. Tr.	Gran. hyal.	R. B. C. Many for two days after operation.
			2/ 4/13	8	995	.....			
			2/ 6/13	16	750	.....			
			2/12/13	32	630	.....			
			2/13/13	31	660	.....	2%		
			2/15/13	32	1.040	.....			
			2/21/13	32	1.000	.....			
			2/26/13	32	950	.....	V. H. Tr.		
			3/ 6/13	8	1.500	.....			
			3/13/13	16	930	.....			
			3/17/13	32	700	.....			
			3/19/13	32	900	.....			
			5/ 8/13	32	1,350	.....			

CHRONIC PARENCHYMATOUS NEPHRITIS

	Urine				
Blood Pressure	Reaction	Phenolsulphonephthalein Per Cent.	Date	Disease	Result
240 (S) to 80 (S) (term).	Acid	55 45 56	10/27/12 11/13/12 3/ 5/13	Chronic interstitial nephritis.	Died
170 (S) to 200 (S)	Acid	45	10/26/12	Chronic interstitial nephritis. This patient had hyperglycemia and persistent glycosuria. Regarded as a case of dyspituitarism.	Improved
205 (S)	Acid	26	10/ 3/12	Chronic interstitial nephritis.	Improved
130 (S)	Acid	None made.	....	Chronic par. neph. (Some edema. Chronic pul. tuberculosis. Always fever.)	Died
....	Acid	F. Tr.	11 2/12	Chronic interstitial nephritis. (Atony of bladder.)	Improved
130 (S) 80 (S)	Acid	36	11/ 2/12	Had marked amyloid change in kidney, liver and spleen at necropsy.	Died
220 (S) 250 (S)	Acid	Less than 5 Trace 1 1	11/22/12 12/ 3/12 1/ 6/13 1/15/13	Chronic interstitial nephritis. (Necropsy showed extreme art. scl. of bl. ves., kidney, etc.)	Died
180 (S) to 200 (S)	Acid	13	11/ 4/12	Chronic interstitial nephritis. (Empyema of frontal sinus. secondary diagnosis.)	Died
....	Acid	10 5 3	12/ 6/12 1/ 6/13 2/ 3/13	Chronic interstitial nephritis. (Secondary anemia.)	Improved
Within normal limits	Acid	32 38	1/ 9/13 1/21/13	Chronic interstitial nephritis. (Chronic card. valv. dis.)	Improved
200 (S)	Acid	16 10	1/ 9/13 1/24/13	Chronic interstitial nephritis. Congenital cystic kidney and hydrothorax.	Improved
200 (S)	Acid	33	1/14/13	Chronic interstitial nephritis.	Died
220 (S)	Acid	5 Trace	1/16/13 11/25/13	Chronic interstitial nephritis.	Improved
170 (S)	Acid	57	1/16/13	Chronic interstitial nephritis. (Diabetes not severe but may be primary disease.)	Improved
180 (S)	Acid	11 76	1/25/12 2/13/13	Chronic interstitial nephritis. (Acute tonsillitis.)	Improved
....	Acid	48	2/19/13	Chronic interstitial nephritis. (Acute cardiac dilatation.)	Improved
190 (S)	Acid	40 23 13 16 10 13 31 29 66 60 46 44	10/16/12 11/12/12 12/10/12 12/23/12 1/10/13 1/27/13 2/10/13 2/25/13 4/ 2/13 4/21/13 5/ 6/13 5/24/13	Chronic parenchy. nephritis. Jan. 30, 1913, had double decapsulation of kidneys. Since then edema has disappeared. Developed symptoms since Feb. 19, 1913, of pul. tuberculosis with fever. Discharged July 8, 1913. Still fever.	Improved

TABLE 1.—CHRONIC INTERSTITIAL NEPHRITIS.

Case	Name	Sex	Date	Amlase	Urine				
					Quant. c.c.	Sp. Gr.	Albumin	Casts	Blood
18	M. B.	F.	2/ 6/13	16	1.355	1.016	H. Tr.	Gran., hyal.	0
			2/ 8/13	16	1,200	1.022			
19	E. J.	F.	2/ 4/13	2	1.150	1.010	V. H. Tr. 0.2% to 1%	Very many waxy hyal., gran.	0
			2/ 5/13	2	1,400	.....			
			2/12/13	0	1,160	.....			
			2/21/13	0	1,000	.....			
			3/ 6/13	0	1,005	.....			
			3/13/13	0	900	.....			
			3/16/13	0	520	.....			
20	C. W.	F.	2/ 9/13	2	1,530	.....	H. Tr.	Hyal.	Few R. B. C.
			2/10/13	2	1,470	.....			
			2/21/13	2	1,010	.....			
21	K. D.	F.	2/ 9/13	8	2,100	1.023	V. H. Tr.	Hyal., gran.	Much blood.
			2/10/13	8	1,120	1.017			
22	J. M.	M.	2/14/13	16	1,170	.....	V. H. Tr.	Hyal., gran.	0
			2/16/13	16	1,020	.....			
23	C. S.	M.	2/19/13	8	520	1.025	V. H. Tr.	Hyal., gran.	Many R. B. C.
24	B. G.	F.	2/ 8/13	4	255+	.....	Tr.	0	Few R. B. C.
25	N. F.	M.	3/ 6/13	8	1.350	1.010	V. H. Tr. Tr. V. H. Tr.	Hyal., gran. (many)	Few R. B. C.
			3/11/13	0	1,950	1.016			
			3/12/13	8	1,800	.....			
			3/13/13	8	1,260	.....			
			3/17/13	0	1.520	.....			
26	J. F. G.	M.	3/ 7/13	8	1,500	1.012	H. Tr.	Hyal., gran. (many)	0
			3/12/13	8	1.450	1.020			
			3/18/13	16	700	.....			
27	S. M.	F.	3/12/13	0	950	.....	3%	Hyal., gran.	Few R. B. C.
			3/18/13	0	700	.....			
28	P. C.	M.	3/22/13	0	1,170	.....	Tr.	Hyal., gran.	0
29	C. M.	M.	4/ 9/13	2	1,800	1.010	H. Tr.	Hyal.	R. B. C. much pus.
			4/12/13	0	1,870	.....			
			4/16/13	2	2,240	1.022			
30	D. C.	M.	3/ 4/13	4	1,480	1.015	V. H. Tr.	Hyal., gran.	R. B. C. few.
31	R. C.	M.	5/14/13	4	900	1.013	H. Tr.	Hyal., gran.	0
32	S. C.	M.	5/ 1/13	4	1,250	.....	Tr.	Hyal., gran.	R. B. C. few.
			5/15/13	4	1.500	.....			
33	J. Y.	M.	5/22/13	2	1,500	.....	H. Tr.	Hyal., gran.	R. B. C. many
			6/15/13	2	1,200	.....			
34	J. M.	M.	5/15/13	2	1,400	1.015	H. Tr.	Hyal., gran. and fatty.	R. B. C. many.
35	T. V.	M.	1/25/13	8	905	1.019	Tr.	Hyal., gran.	0

HRONIC PARENCHYMATOUS NEPHRITIS—(Continued)

Urine					
Blood Pressure	Reaction	Phenol-sulphonephthalein Per Cent.	Date	Disease	Result
210 (S)	Acid	33 69	2/ 7/13 3/10/13	Chronic interstitial nephritis. (Chr. card. valv. dis.)	
130 (S) 160 (S)	Acid	3 11 10	1/ 6/13 1/27/13 2/ 3/13	Chronic interstitial nephritis. Necropsy: Chronic dif. neph. (amyloid.) Aortic and mitral endocarditis. (Regurgitation and stenosis.)	Improved
....	Neutral	F. Tr. F. Tr.	1/ 3/13 2/14/13	Chronic interstitial nephritis.	Unimproved
180 (S)	Neutral	58	2/ 7/13	Chronic interstitial nephritis.	Improved
215 (S)	Acid	35	2/13/13	Chronic interstitial nephritis.	Improved
200 (S)	Acid	53	....	Chronic interstitial nephritis. Cardiac hypertrophy. Tabes dor.	Improved
240 (S)	Acid	28 65	2/17/13 3/ 5/13	Necropsy: Chronic dif. neph. Hemorrhage into cerebrum.	Died
Above 160 (S)	Acid	12 19	3/ 4/13 3/ 8/13	Chronic interstitial nephritis.	Improved
....	Acid	44 42	3/10/13 3/22/13	Chronic interstitial nephritis.	Improved
....	Neutral	None made.	....	Chronic par. nephritis.	Improved
150 (S)	Acid	13	4/19/13	Acute nephritis; bronchitis.	Cured
....	Acid	Trace Trace Trace	4/ 8/13 4/15/13 5/12/13	Pyelitis (bilateral). Uremia. Delayed excretion urine, bloody, from left ureter.	Died
....	Acid	28	4/27/13	Chronic parenchymatous neph.	Improved
....	Acid	15	5/ 9/13	Chronic interstitial nephritis.	Died
....	Acid	52	3/ 7/13	Chronic interstitial nephritis.	Improved
180 (S)	Acid	5 Trace	5/20/13 6/13/13	Chronic interstitial nephritis.	Died
....	Acid	24 16	5/13/13 6/13/13	Chronic interstitial nephritis. (Chr. card. valv. dis.)	Died
140 (S)	Acid	70 54	1/13/13 1/23/13	Chronic interstitial nephritis.	Died

"little albumin" give subnormal "d" readings; eleven cases which have "much albumin" give subnormal "d" readings, Case 12 showing both; seven cases which have "much albumin" give normal or high normal "d" readings; while two cases in which there was little albumin give low normal "d" readings, and both these cases give normal phthaleins.

Cases 1, 17 and 25 do not permit of classification as regards this subject, as all have shown much albumin with varying "d" readings.

No hard-and-fast conclusions can be drawn from these figures, both because the method of estimating the quantity of albumin is purely an arbitrary one, and because the number of cases is not sufficient, but the results are at least suggestive of the fact as observed by other investigators that in cases of nephritis with high albumin content there is a greater tendency to normal or high normal "d" values than in those with small albumin content, when the "d" readings are almost invariably subnormal, and further, in those urines, when in spite of a high albumin content, persistently subnormal "d" readings are found, it can be assumed that the functional damage has been all the more severe. In all cases we must not forget the possible effect of blood if that be present. Also the presence of pus of extra-renal origin as a factor in the production or intensification of the albumin test must not be overlooked, in view of what Neuman[16] asserts, that is, that pus has no influence on the "d" readings.[32]

The question of dilution and its effect on the quantitative estimation of amylase is one that has been the subject of much discussion on the part of many observers. Wynhausen,[13] Marino,[15] Corbett,[8] Rosenthal[14] and Benczur[12] argue that its influence is a very limited one, and in the range of normal twenty-four-hour urines no appreciable effect is noted on the "d" readings. Wynhausen[13] quoted a case in which two readings were identical in the case of a patient who had 700 c.c. of urine, specific gravity 1.015, and a month later had 2,500 c.c. of urine, specific gravity 1.015. All the other authors mentioned above quote many similar cases. They agree that only in cases of extreme variations in amount do the "d" values change. One of my patients who had shown a reading of 32 on two occasions, only five days apart, with urine quantity amounting to 940 c.c. and 1,300 c.c., showed fifteen days later a reading of 8, with a urine quantity of 4,000 c.c. This was a patient who had an exophthalmic goiter (Case 10, Table 3), whose condition throughout her stay changed very little. In each instance the "d" reading was within normal limits, although the effect of the diuresis on the last "d" reading can readily be seen. Extremely low amounts of urine (under 500) are found only, as a rule, in renal and cardiac condition, and the renal cases in spite of this show a low "d" reading. If in a case of this kind the reading should be 8, for instance, in view of the concentration of the urine we would be justified in assuming that were the quantity of the urine within normal limits, the reading would be lower. The effect of concentration on the "d" value may be noted in Case 7, Table 2. Here we have an approximately normal excretion of phenolsulphonephthalein and a high normal "d" reading, 32 on three occasions. It is probable that urine within normal limits in this case would have brought the reading to a lower "d" worth. In general, it may be assumed that only when a urine is abnormally large or abnormally small in quantity allowance need be made for dilution or concentration in judging the value of the actual "d" reading.

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[32] Neuman's work appeared after this investigation had been concluded and the tables made out. Allusions to his work have been included only as they could be added to the text and had reference to what has already been written. His work on the effect of dilution on the "d" reading has not been alluded to as no time to study its application has been available.

Rosenthal[14] has made an attempt to estimate what he terms the "absolute diastatic strength" of the urine. This he does by multiplying the twenty-four-hour total by the "d" reading and then dividing by 2: for example, daily output 1,500 c.c., 0.2 c.c. of urine digests 2 c.c. 0.1 per cent. starch solution, therefore the absolute diastatic strength =

$$\frac{1{,}500 \times 10}{2} = 7{,}500, \text{ or } 500 \text{ per cent. concentration.}$$

I do not see that anything is gained by this method, and as Corbett aptly comments, "the results would vary out of all proportion to slight changes in the daily excretion," which in Rosenthal's series they do.

Another factor to be considered is the influence of fever on the "d" values, and here all observers agree that very high readings are found in acute infectious diseases. Rosenthal[14] demonstrates the influence of high temperatures in a case of nephritis which developed lobar-pneumonia. During the febrile period amylase was present in normal amounts; after subsidence of the fever no amylase could be found in the urine, while the clinical picture was at all times that of nephritis.

Having discussed the various conditions which may affect the action of amylase in the urine and having seen that in normal individuals in a twenty-four-hour specimen the "d" readings vary within narrow limits, it is appropriate at this point to summarize briefly actual figures obtained for the "d" values of normal twenty-four-hour urine specimens. Wohlgemuth,[7] in a large series of normal cases, says it varies between

$$d\frac{38^\circ}{30'} = 16 \text{ to } 32$$

never exceeding 64. Corbett,[8] working with slightly different dilutions, gives 6.6 to 33.3 with an average of from 10 to 24. Rosenthal,[14] whose method of calculating his readings is different, gives 10 to 25 when his results are translated into terms of the original Wohlgemuth method.

From repeated examination of eight normal cases and many other cases whose clinical condition gave no reason to suspect altered "d" readings, I have reached the conclusion that "d" = 8 to 32 is the normal range for twenty-four-hour urine. The large majority of the readings were between 16 and 32, as given by Wohlgemuth. I have never had a normal urine in which a reading of 64 has been reached.

Coming to the study of altered amylolytic power of the urine observations in the literature, so far it has been confined mainly to four conditions, that is, nephritis, diabetes, pancreatic disease and the so-called diabetes insipidus. Many other conditions have also been investigated, but the most positive and important results have been obtained in these four conditions.

NEPHRITIS

This includes all forms of the disease ranging from the acute type to the chronic (tubular, vascular or mixed) types, and includes also such conditions as pyelitis and renal calculus. Hirata,[33] working under Wohlgemuth's direction, produced sublimate, chromate and uranium nephritis in rabbits, estimating the amylolytic power of their urine before and after the production of nephritis. He found that the "d" values in all forms of nephritis were markedly decreased with a coincident rise on the "d" value of the blood, which was not always as marked as that shown in the urine. In view of the fact that these forms of experimental nephritis interfere mainly with tubular function, it would seem probable that amylase was excreted in largest quantities via this route.

This work on animals has been further substantiated by the investigations on patients suffering from various forms of nephritis. Wohlgemuth,[17] Wynhausen,[13] Marino,[15] Rosenthal,[14] and more recently Corbet[8] and Neuman[16] give distinctly low "d" readings for nephritis in general. Benczur[12] does not agree with the above-mentioned investigators, although he admits low readings in some of his cases of nephritis. He reports only eleven cases and five of these showed low "d" values. Two of the other cases showed very high readings. Benczur comes to the conclusion that no reliable information can be drawn from the test. It is interesting to note in this connection that although Benczur could not find any "essential" difference between $d\frac{37°}{24\text{ hr.}}$ readings of individual specimens and those of twenty-four-hour specimens, his five cases of nephritis with low readings were all twenty-four-hour specimens, while the other specimens examined, taken in hunger periods, when as Wohlgemuth shows, the "d" readings are highest, all give much higher amylase values.

Certainly the preponderance of evidence so far adduced demonstrates that in the large majority of so-called nephritides the amylase value of twenty-four-hour specimens of urine is markedly below normal and in very few of the remaining cases does it exceed low normal limits. It must be admitted, on the other hand, that undoubted cases of severe chronic diffuse nephritis, proved by necropsy, and by the presence of every characteristic clinical symptom, have shown normal "d" readings, but these cases may also show one of the other functional tests to be normal.

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[33] Hirata, G.: Biochem. Ztschr., 1910, xxviii, 23.

In all of the thirty-five cases of renal disease shown in Table 1, the "d" value of the urine has been estimated one or more times. In all but two of the cases the phenolsulphonephthalein test of Rowntree and Geraghty has been made, and in the majority of instances on the day preceding the "d" estimation.

A word as to the technic of performing the phenolsulphonephthalein test in the First and Second Medical Divisions of the Presbyterian Hospital may be of service. The patient is given 200 to 300 c.c. of water twenty minutes previous to the administration of 6 mg. of the drug, which is given intramuscularly in all but a few instances, when it is given intravenously. The time of first appearance is noted. The specimen for this can usually be obtained by getting patient to void; if this is not possible, a catheter is used. Then the urines collected the first and second hours are estimated separately. The figures given are the totals of the first- and second-hour amounts. The time of appearance and the separate amounts for each hour are not deemed of sufficient importance in their relation to the "d" values to be tabulated. With the estimation of amylase, the quantity, specific gravity, reaction, albumin, casts and blood were noted in all twenty-four-hour specimens, not only on day of "d" estimation, but at intervals during their stay in the hospital. Albumin and casts are tabulated as an average finding in several examinations during the test periods or albumin as a separate finding when its relation to the "d" reading is important.

The diagnoses appended are clinical and made at the time of discharge of patient. Secondary conditions and necropsy findings are given when they occur.

From Table 1, if we consider eight as low normal limit, it will be seen that twenty-three of the thirty-five cases of nephritis, or 65.7 per cent., show persistent subnormal or absent "d" values. If we compare these values with the phenolsulphonephthalein readings we find that twenty of the corresponding cases also show a lowered phthalein excretion, assuming anything below fifty to be subnormal.[34] Of the remaining three cases, one (27) was a severe case of nephritis and the phenolsulphonephthalein test was not made, as it was not deemed advisable to disturb the patient; while in the other two cases (14 and 32), which showed phenolsulphonephthaleins of 57 per cent. and 52 per cent., respectively, with "d" readings of four in each case, no definite theory can be advanced to explain the discrepancy, unless, as in Case 14, the mild degree of diabetes and secondary anemia can explain it. Low "d" readings in these conditions having been found by other observers, Marino,[15] Neuman,[16] Wynhausen,[13] etc. Case 32, however, cannot be explained on any such basis.

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[34] Cases 15 and 24 are here included as the later high readings for phenolsulphonephthalein were not explained clinically.

Of the twelve cases which do not show subnormal "d" values in every estimation, three show it in two or more readings and their average would be subnormal. Two of these three cases, namely, Cases 8 and 25, show low phenolsulphonephthaleins, whereas the other case (1) shows one lowered phthalein and two readings above normal. This latter case was one of severe nephritis and the patient died in a uremic condition.

This leaves nine cases of nephritis, as evidenced by clinical signs, in which there was a low normal or normal "d" reading. Of these, one (4) did not have the phenolsulphonephthalein test made. Of the remaining eight, five, that is, Cases 12, 16, 18, 22 and 26, gave normal "d" readings and slightly subnormal phthalein readings, while three cases, namely, 21, 23 and 35, gave normal "d" and phenolsulphonephthalein readings.

To summarize, then:

In thirty-three cases both tests were made.

In twenty-two cases subnormal readings were shown for both tests.

Three of the remaining eleven show diminished "d" with normal phenolsulphonephthalein (Cases 1, 14 and 32).

Five show diminished phenolsulphonephthalein with normal "d" readings.

Three of these cases (16, 18 and 26) show a diminution of phthalein, which was very little below normal, Case 18 having at one time 69 per cent. The remaining three agree in that they show normal "d" and phenolsulphonephthalein readings.

Case 17, J. T., calls for more detailed comment. I have included this case among those that give a low reading for both tests, because at the height of his kidney condition they both showed very low readings. This was in the latter part of January. At that time the edema was extreme, the urine quantities very small, blood-pressure was high and the patient was rapidly going into uremia. January 30 a double decapsulation of the kidneys was made, and from that time on until July, when he was discharged, his kidney condition improved remarkably. The edema disappeared, the urine increased and the blood-pressure fell. Both functional tests came from extremely low readings to high normal readings; one amylase reading, March 6, 1913, showed low normal limit, but immediately rose again. The patient developed pulmonary tuberculosis a month after the operation, and although this improved slightly, it still persisted at the time of his leaving the hospital. Three high normal "d" readings were obtained before fever developed, which was persistent but slight.

In Cases 1, 8 and 25, we find that there is not absolute agreement in all of the "d" readings; taken as an average, they are below normal, and should be interpreted as such. In Case 1 it must be noted that the phthalein average was normal.

It is of interest further to note that in every case when the "d" value was normal with small amounts of albumin the phenolsulphonephthalein was also normal.

In Case 8, it is of interest to note that the reading of 16 was obtained during a period of marked clinical improvement, whereas the other readings were obtained during the reverse condition.

As regards the relationship existing between the "d" reading and the severity of the nephritis, I am unable to draw any definite conclusions. In this connection, Wynhausen[13] states that the lower the "d" reading the more severe the nephritis. Some patients with low and in some cases absent "d" readings, were discharged apparently improved. Of course, there has not been sufficient time in some cases to determine what the outcome will be, while in others there is no data as to what may have occurred after the patient left the hospital.

On the other hand, three patients with normal or high normal "d" readings have died. In one of these cases (No. 4) death was probably due to complicating disease. Excluding this case, it will be seen that nine of the eleven patients who died had low "d" readings.

CARDIAC DISEASE

In Table 2 nineteen cases of cardiac disease are tabulated. In some of these at certain times during which the patients stayed in the hospital, there were marked evidences of acute myocardial insufficiency. In all of the nineteen cases phenolsulphonephthalein and "d" readings were made, and in seven of the cases two phthalein readings were made, one at the time of acute decompensation and a second one later. Six of these cases showed low readings at the time of decompensation and normal readings later. This was rather a striking feature of these cases, a fact that has already been pointed out by Rowntree, Geraghty and Fitz,[35] who produced varying grades of chronic passive congestion of the kidneys in dogs, and found in the severe types of congestion a marked diminution in the phthalein output. This, Rowntree and Fitz[36] later confirmed in their clinical findings in a series of cardiac cases, which at the time of acute

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[35] Rowntree, Geraghty and Fitz: The Archives. Int. Med., 1913, xi, 121.

[36] Rowntree and Fitz: The Archives Int. Med., 1913, xi, 258.

TABLE 2.—CHRONIC CARDIO-VALVULAR

Case	Name	Sex	Date	Amylase	Urine				
					Amt. c.c	Sp. Gr.	Albumin	Casts	Blood
1	M. F.	F.	10/31/13	16	1.620	1.015	0	0	....
2	F. P.	M.	1/ 8/13	128	350+	1.025	H. Tr.	Hyal., gran.	Much
3	J. F.	M.	1/10/13	16	1,470	1.030	Trace	Hyal., gran.	Few R. B. C.
4	J. C.	M.	1/13/13	8	2.400	1.020	0	0	0
5	F. C.	M.	1/12/13 1/15/13	16 32	1,730 1.290	1.025	H. Tr.	Hyal., gran.	0
6	J. H.	M.	1/16/13	16	1.530	1.015	F. Tr.	Hyal.	0
7	F. R.	M.	1/18/13 1/31/13 2/ 6/13	32 32 32	520 300 450	1.030	V. F. Trace	0	0
8	S. C.	F.	1/22/13 2/17/13	32 64	605 1.105	1.029	V. H. Trace F. Tr.	Hyal., gran.	R. B. C. few
9	F. S.	F.	1/25/13	16	680	1.017	F. Tr.	0	0
10	R.	M.	2/ 5/13	2	1,150	.....	Trace	0	0*
11	J. V.	M.	2/ 4/13	8	3,210	1.030	H. Tr.	0	0
12	S. P.	F.	2/12/13 2/14/13	32 16	450 1,025	....	V. F. Trace	Hyal	0
13	L. D.	F.	2/16/13	16	910	.....	V. F. Trace	0	0
14	D. C.	M.	2/17/13	32	1,745	.....	F. Tr.	Hyal.	0
15	P. D. L.	M.	2/18/13 3/11/13	16 16	880 1,700	....	H. Tr.	Hyal., gran.	Many R. B. C.
16	D.	F.	3/ 2/13 3/13/13	8 8	1,000 930	....	V. F. Trace	Few hyal.	0
17	M. F.	F.	4/ 8/13 4/ 9/13	16 16	1,350 1,400	1.020	F. Tr.	Hyal., gran.	Occ. R. B. C.
18	A. W.	F.	4/ 9/13	16	970	1.025	F. Tr.	0	0
19	K. W.	F.	1/15/13	16	440	1.015	H. Tr.	Coarsely gran., hyal.	Mod. R. B. C.

* Blood-pressure, systolic, 110.

Urine			
Phenol-sulphone-phthalein Per Cent.	Date	Diagnosis	Result
65	10/18/12	Chronic cardio-valvular disease. (This was during an acute attack of decompensation.)	Improved
8	11/ 5/12		
52	11/11/12		
65	12/ 6/12		
33	1/ 7/13	Chronic cardiac hypertrophy. Cardiac dilatation. Emphysema of lungs.	Died
43	1/ 8/13	Chronic cardio-valvular disease.	Died
53	1/11/13	Chronic cardio-valvular disease.	Improved
35	12/19/12	Chronic cardiac insufficiency and myocarditis.	Improved
62	12/23/12		
32	12/30/12	Chronic cardio-valvular disease; aortitis.	Improved
57	1/14/13		
47	1/16/13	Chronic cardio-valvular disease; mitral regurgitation; aortic regurgitation. (Necropsy diagnosis same as clinical.)	Died
4	1/20/13	Chronic cardiac insufficiency; hydrothorax.	Improved
43	2/15/13		
64	1/23/13	Chronic cardio-valvular disease; acute endocarditis (fever.)	Died
51	2/ 2/13	Chronic cardio-valvular disease; subacute articular rheumatism.	Improved
41	2/ 3/13	Chronic cardio-valvular disease; auricular fibrillation; aortic roughening and stenosis.	Improved
20	2/ 2/13	Obesity and fatty heart.	Improved
58	2/10/13		
84	2/14/13	Chronic cardio-valvular disease; cardiac hypertrophy and dilatation.	Improved
28	2/16/13	Chronic cardio-valvular disease; septicemia (fever); acute pericarditis.	Died
21	2/17/13	Chronic cardio-valvular disease; cardiac hypertrophy and dilatation.	Improved
65	3/ 7/13		
56	3/ 1/13	Chronic cardio-valvular disease.	Improved
53	3/12/13		
64	4/ 7/13	Chronic cardio-valvular disease.	Improved
48	4/ 7/13	Chronic cardio-valvular disease; hydrothorax.	Improved
34	1/17/13	Chronic cardio-valvular disease.	Died
Appear- nce after ne hour.			

insufficiency showed low phthalein readings, with subsequent normal readings when the symptoms of decompensation cleared up and there was no concomitant nephritis.

In only one case in Table 2 have synchronous "d" and phenolsulphonephthalein readings been made during the time of decompensation, and later when compensation was restored. In this case (No. 8), when the phthalein was 4 per cent. the "d" value was 32, while nearly a month later the phthalein had increased to 43 per cent. and the "d" reading to 64. In another case (No. 19), during decompensation, when the phthalein was low, 34 per cent., the "d" reading was 16, or normal.

In view of the fact that at the time of acute decompensation with diminished phenolsulphonephthalein excretion there is nearly always a large amount of albumin and many red blood-cells, we would not expect to find low "d" readings, and in the few cases observed this has proved to be the case; in fact, it has been rather high normal. So that we must conclude that the "d" reading shows very little if anything as regards functional activity during the periods of decompensation. If it can be shown that during the period of passive congestion, the urine, in spite of the presence of albumin and blood, gives a reading of 8 or 16, and then later when these two constituents are diminished or absent and the heart condition has improved, the reading is still the same or perhaps increased to 32, we might readily assume that what in other circumstances would be taken for a normal reading had really been an expression of impaired function.

Generally speaking, twelve out of nineteen cases show normal phenolsulphonephthalein (after the period of decompensation, readings of 48 per cent. and 47 per cent. included) and also normal "d" readings. Of the remaining seven cases, three (3, 8 and 11) showed only slightly impaired phthaleins with normal "d" readings and in none of these cases were further phenolsulphonephthalein tests made.

Three cases showed phthaleins ranging from 28 to 34 and normal "d" readings. Of these last three cases, Case 2 showed very high "d," 128, but there was much blood in the specimen. Case 19 showed marked passive congestion of lungs and liver as well as kidneys during the stay in the hospital, and while the "d" reading is 16, the possible influence of concentration of the urine, blood and albumin must be noted. The third case in this group is one where the phenolsulphonephthalein was 28 per cent. and the "d" reading 16. Here there is a possible influence exerted by fever.

There is one atypical case in this group, and that is Case 10. Phthalein reads 51 per cent. and "d" 2. That there was any renal involvement in this case was certainly not demonstrable clinically, either at the time of admission to the hospital or at any subsequent time. It must remain unexplained.

In this series of cardiac cases there are only three in which the influence of urinary concentration should be considered, namely, Cases 7 and 19. In both these cases we may consider a lower reading than that given to be possible, but the question as to what the "d" readings might have been, had the urine quantities been larger, was not determinable in either case. In Case 11, with 3,210 c.c. of urine and a reading of 8, a higher reading, let us assume, to 16 would still have been in accord with what other cases of this series show.

In Table 3 thirteen cases of varied clinical conditions are tabulated. In this table each case or each group of cases must be considered separately.

DIABETES

First of all let us consider diabetes. Only two cases are to be found in this table, while the other two are found in Table 1. It must be acknowledged that both cases in Table 1 cannot be considered as pure cases of diabetes. There was doubt in the minds of those who studied Case 14, R. P. (Table 1), as to whether the nephritis or glycosuric condition was the primary one. Also in Case 2, L. K. (Table 1), the question not only of nephritis but of dyspituitarism entered into the consideration. The glycosuria in this case was small but persistent, and failed to yield at all to dietary measures. We find that both these cases showed subnormal "d" readings with normal amounts of urine. The phthalein in one case, that of L. K. (Case 2, Table 1), was a shade under the normal, while with R. P. (Case 14) it was normal. The clinical findings all pointed to an underlying chronic nephritis, and for this reason I have classed them as nephritics.

Case 6, J. C., and Case 12, Wm. McG. (Table 3), were quite different, as the patients undoubtedly suffered from a primary diabetes mellitus, with large sugar outputs, and in Case 6 multiple furunculosis with diacetic acid and acetone in the urine. The urine quantity was low in Case 6, but a portion was lost; in fact, twenty-four-hour specimens were very hard to obtain. The patient had a normal "d" reading with little albumin and little blood, as did also Wm. McG.

No conclusions from these four cases are justified.

Foster,[4] as early as 1867, investigated amylase in the urine of diabetics, and concludes that its value does not exceed normal limits. Leo[37] and Benderesky[38] found amylase increased in urine of diabetics. Lépine[5] found it decreased in the same disease. Enriquez and Binet[39] found the amylase values high in diabetes, decreasing as the sugar content of the urine decreased. Loeper and Ficai[40] found it decreased, while

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37. Leo: Verhandl. d. VII. Kongr. f. inn. Med., 1888.
38. Benderesky: Virchows Arch. f. path. Anat., 1890, 121, 554.
39. Enriquez and Binet: Compt. rend. hebd. Soc. de biol. de Paris, 1908, lxv, 577.
40. Loeper and Ficai: Arch. de méd. expér. et d'anat. path., 1907, xix, 722.

TABLE 3.—

Case	Name	Sex	Date	Amylase	Urine				
					Amt. c.c	Sp. Gr.	Albumin	Casts	Blood
1	A. N.	F.	10/22/12	4	Incomplete	1.020 to 1.032	V. F. Trace	Few hyal.	0*
2	J. W.	M.	10/30/12	8	1,590	1.016	V. F. Trace	Hyal., gran.	0
3	C. F.	F.	12/ 4/12	64	800	.....	V. F. Trace	0	0
4	M. G.	F.	12/ 3/12 12/ 6/12	32 32	1,600 1,450	....	0	0	Many pus cells Alkaline (reaction) alkaline
5	C. W.	F.	12/ 4/12	32	840	1.020	0	0	0
6	J. C.	F.	12/13/12	16	360+	1.024	Trace	Gran., hyal.	Sugar. Few R. B. C.
7	T. M. 7years	M.	1/15/13	2	830+	1.010	0	0	0
8	T. T.	M.	1/21/13	32	2,500	1.010	F. Tr.	Hyal., gran., epith.	Bile
9	A. D.	F.	1/22/13	8	1,545	1.020	F. Tr.	Hyal., gran.	Few R. B. C.
10	D. M.	F.	1/25/13 1/30/13 2/25/13	32 32 8	1,300 940 4,000	1.015	V. F. Trace	Occ. hyal.	0
11	E. B.	F.	2/28/13	8	550+	1.025	V. F. Trace	Hyal., gran.	Very few R. B. C.
12	Wm. Mc C.	M.	3/12/13 3/18/13	16 16	1,300 1,300	1.040	Trace	0	0
13	G. K.	M.	5/30/13	32	465	1.030	V. F. Trace	Occ. gran.	0

* Blood-pressure, 130 systolic.

scellaneous Cases

Urine		Diagnosis	Result
Phenol- ulphone- hthalein er Cent.	Date		
41 63	10/25/12 10/30/12	Brain tumor. (No necropsy.)	Died two days after bilateral decompression
24	10/26/12	Multiple myelomata (Bence-Jones bodies in urine). Fractured ribs.	Improved
None made	....	Syph. arthritis knee.	Improved
None made	....	Pyelitis. Cystitis of pregnancy.	Improved
None made	....	Exophthalmic goiter; glycosuria.	Improved
None made	....	Diabetes mellitus; multiple staphylococcic abscesses (fever).	Improved
None made	....	Diabetes insipidus.	Improved
None made	....	Hypertrophic cirrhosis of liver; cholangitis; ascites.	Improved
58	1/21/13	Complete abortion; albuminuria of pregnancy.	Improved
69	2/12/13	Exophthalmic goiter.	Improved
None made	....	Asthma.	Improved
None made	....	Diabetes mellitus; syphilis.	Improved
47	5/26/13	Chronic bronchitis.	Improved

Clark[41] found it absent. These were the most important contributions to the literature on this subject prior to 1908, when Wohlgemuth proposed the "starch iodin" method. All investigations prior to this had lacked reliable and uniform methods of estimating amylase, consequently these results are questionable.

Wohlgemuth[17] with four cases, Wynhausen[13] with forty, Rosenthal[14] with ten and Marino[15] with ten, find generally low readings in diabetes, some cases showing entire absence of amylase. Corbett[8] confirms this. Beneczur[12] denies any variation from normal. None of the preceding writers seem to appreciate the possible effect of the tremendous diuresis which usually accompanies this disease, as a factor in lowering the "d" reading, or if they do, they merely add that there seems to be no relationship. Corbett[8] does, but in spite of this, insists on subnormal readings for the majority of cases under treatment. Wynhausen[13] says that the lower the "d" reading the more severe the disease and the higher the reading the milder the disease. Another very important complicating factor, which is so often found in diabetes, is nephritis, and this in itself would account for low "d" readings. Wynhausen[13] and Rosenthal[14] acknowledge its presence in the large majority of their very low "d" readings, but fail to appreciate its importance. Marino[15] also merely alludes to it. Even in those cases in which no urinary evidences of nephritis are present, we cannot exclude varying degrees of kidney damage as evidenced, for instance, by decreased permeability for sugar itself, increased blood-pressure, etc.

In view of the great importance of these two factors, namely, extreme diuresis and nephritis, on the values of the "d" readings apart from any other condition, it does not seem justifiable in the light of our present knowledge to attribute the low "d" readings or even the absence of amylase to diabetes *per se*, but rather to regard them as evidences of a complicating condition.

Case 2, L. K., and Case 14, R. P. (Table 1), with low "d" readings, are certainly suggestive of the above, particularly when contrasted with Case 6, J. C. and Case 12, Wm. McG. (Table 3), who, without evidence of renal disease, give normal "d" readings.

Diabetes Insipidus.—Case 7, T. M. (Table 3), a child aged 7, is the only case of the kind that I encountered. Strauss[42] reported two cases in which not only was there no amylase found, but also no pepsin. The absence of the latter had only been met twice before, once in a case of uremia and the other in a case of carcinoma of the stomach. Rosenthal[13] reports a case in which he also failed to find amylase in the urine, except

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41. Clark: Glasgow Med. Jour., 1905, June, 632.
42. Straus, H.: Deutsch. med. Wchnschr., 1912, iv, 163.
43. Rosenthal, A.: Berl. klin. Wchnschr., 1912, xlix, 1265.

in an occasional examination, when it was greatly diminished. Benczur[12] reports one case in which it was present in normal amount. Braunschweig,[44] working in Straus' clinic, has also failed to find pepsin in the urine of such patients. The case (No. 7) reported in Table 3 shows the amylolytic ferment to be greatly diminished.

M. G. (Case 4, Table 3) was not included under the nephritics, as the condition was confined to the right kidney alone, and at the time of these examinations there was no definite evidence of kidney involvement under cystoscopic examination. This evidence was present one month later.

A. N. (Case 1, Table 3) shows a possibility of some renal involvement, but aside from a very faint trace of albumin and a few hyaline casts, there was no definite evidence from a clinical standpoint. It must be regarded as an unexplained case of low "d" reading. The patient died two days after bilateral decompression; no tumor was found; there was no necropsy.

T. T. (Case 8, Table 3) had bile in the urine, and is interesting from the standpoint of what Wohlgemuth[45] has shown, namely, that bile in small amounts accelerates amylolytic action, while in large amounts it inhibitis the action.

It is to be regretted that no cases of pancreatic disease have been studied in view of the tremendously high "d" readings so uniformly found in these cases.

CONCLUSIONS

1. The amount of amylase in the twenty-four-hour specimen of a normal individual estimated by the Wohlgemuth method varies within very narrow limits, and for a given case is almost a constant factor.

2. The "d" value of the urine, in the vast majority of cases of chronic or acute nephritis, is subnormal or totally absent. In the preceding series of thirty-five cases, 77.1 per cent. show this.

3. Only in extreme variations in concentration under 500 and over 2,500 c.c. can this factor be considered to have appreciable influence on the "d" reading, and under these circumstances due allowance should be made in the interpretation of values of "d" obtained.

4. The majority of normal readings obtained in cases of chronic nephritis were from urines containing considerable albumin, seven out of nine cases with normal readings. This simply confirms the work of other investigators and leads us to assume that the presence of albumin itself increases enzymic activity or in the process of its excretion causes more enzyme to be given to the urine. Allowance must always be made for this factor in estimating the "d" value in nephritic urine.

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[44] Braunschweig: Dissertation, Leipsic, 1910.

[45] Wohlgemuth, J.: Biochem. Ztschr., 1909, xxi, 447.

5. As a test for renal function in nephritis the readings for "d" agree remarkably well with those of the phthalein test, if we adopt a definite normal limit for both tests, namely, 50 per cent. for the latter and "d" = 8 for the former. The adoption of 50 per cent. as low normal limit for the phthalein test is one which I think is pretty well accepted by most clinical observers.

6. The degrees of impairment as indicated by percentages in phthalein readings and graded dilutions in the "d" estimation, do not permit comparison. This could hardly be expected.

7. Cardiac cases with symptoms of decompensation do not show lowered "d" values for urine, while the phthalein test is usually subnormal. The normal "d" reading in these cases is probably due to albumin or blood or both.

8. Final conclusions as to the relative merits of these two tests, both as to the diagnosis and prognosis, must await the results obtained from a larger number of cases. Meanwhile I would urge that the "d" test be given an exhaustive trial with relation not only to the phenolsulphonephthalein test, but also to other tests of renal function.

My cordial thanks are due to Drs. Janeway and Longcope for many valuable suggestions, and to the members of the house staff for their cooperation during the course of this work.

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THE CLINICAL STUDY OF HYPERCHOLESTERINEMIA *

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That lipoidal substances play an important rôle in the animal body is now generally recognized. They occur in practically all the body-tissues and the amounts are increased in sclerotic blood-vessels,[1] in the white plaques of retinitis,[2] in xanthomata, in old infarcts, in caseous tuberculous material and in the cholesteatomatous tumors of the ear and cranial cavity. The activity of certain anesthetics varies with their lipoidal solubility and hemolytic processes may be accelerated or retarded by the presence of lipoids. Quite recently a number of relatively simple methods have been described for determining the amounts of lipoids, and especially of cholesterin, in small quantities of blood or blood-serum. As a result, data concerning the quantity of cholesterin in normal and pathological bloods are now rapidly accumulating. It is the purpose of the present paper to review these recent studies of cholesterinemia and to present a series of personal observations.

The methods used for determining the amount of cholesterin in the blood depend on a variety of principles. Since free cholesterin protects red corpuscles from hemolysis by saponin, it has been proposed to estimate the amount of free cholesterin in the blood-serum by determining the degree to which the serum will protect washed red cells from hemolysis by saponin.[3] In most other methods the cholesterin is first extracted from the blood or serum and the amounts extracted are then determined either by direct weighing, by weighing after precipitation with digitonin, or by colorimetric methods. The extraction is of great importance because cholesterin is present in the blood largely in combination with fatty acids or other substances and the amount extracted depends on the degree to which these combinations are broken up. For this reason the simple extraction of dried blood or blood-serum in the Soxhlet apparatus

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* From the Department of Internal Medicine, University of Michigan, Department of Medicine and Surgery.

* Submitted for publication, July 30, 1913.

1. Windaus: Ueber den Gehalt normalen und atheromatösen Aorten an Cholesterin und Cholesterinester, Ztschr. f. physiol. Chem., 1910, lxvii, 174.

2. Chauffard, A., de Font-Réaulx and Laroche, G.: Nature cholestérinique des plaques blanches rétiniennes dans un cas de rétinite albuminurique, Compt. rend. Soc. de Biol., 1912, lxxiii, 283.

3. Boidin, L., and Flandin, C.: Procédé rapide de diagnostic de l'hypercholestérinémie à l'aide de la saponine, Compt. rend. Soc. de Biol., 1912, lxxii, 28.

uniformly fails to yield the total free and combined cholesterin present. The method which we have used is based on the methods described by Grigaut[4] and by Weston and Kent.[5] In extracting we followed the method of Grigaut, in which a preliminary treatment of the blood-serum with an alkaline alcoholic solution at a high temperature is used to break up the cholesterin compounds. The colorimetric estimation of the amounts of cholesterin subsequently extracted was made according to the modification of Salkowski's test described by Weston and Kent.

TECHNIC

In brief, our procedures were as follows:

Two c.c. of blood-serum were placed in a pressure bottle of 150 c.c. capacity. To this was added 20 c.c. of 1 per cent. solution of potassium hydroxid dissolved in 50 per cent. alcohol. The cover was screwed down and the whole placed in a boiling water-bath for from fifteen to twenty-minutes. After removal from the water-bath, the contents of the pressure bottle were allowed to cool and were then shaken with 50 c.c. of ether. The ether was decanted into a separating funnel and 30 c.c. more of ether was added to the remaining fluid and shaken vigorously as before. This was again decanted into the funnel and any aqueous liquid which separated from the ether was removed. This was then washed with 80 c.c. of distilled water. The ethereal extract, after separation from the wash water, was poured into an evaporating dish and evaporated nearly to dryness, leaving behind the small yellow oily droplets containing the cholesterin. Five c.c. of chloroform (Merck's blue label) was then placed on the evaporating dish and rotated carefully so as to dissolve the oily droplets as completely as possible. This chloroform solution was transferred to a convenient receptacle, and a second 5 c.c. of chloroform was then used to wash the evaporating dish and were added to the first 5 c.c.

The amount of cholesterin in the chloroform solution was determined by comparing its color reaction with those of cholesterin chloroform solutions of known strength. These standard solutions were prepared by dissolving Merck's cholesterin in pure chloroform (Merck's blue label) and by preparing a series of dilutions of varying strength so that the amount of cholesterin in 1 c.c. of chloroform varied from 0.0002 to 0.0004 gm. A set of test-tubes of uniform bore were arranged in a rack and 1 c.c. each of the known solutions of cholesterin were added in ascending series, as was also 1 c.c. of the cholesterin solution prepared from the blood-serum. It was often necessary to dilute the latter so that the amount would fall within the scale of the known quantities. To each tube was now added 0.1 c.c. of concentrated sulphuric acid, and the mixture was thoroughly shaken. After thirty minutes 1 c.c. of chloroform was added to each tube and after being placed for fifteen minutes in a dark room. the color of the unknown solution was compared with that of the known. This method was found to be exceedingly sensitive and differences in the original fluid of 0.00005 gm. per c.c. could be detected. Successive readings from the same serum also gave concordant results, and even after several days' standing, little or no diminution in the amount of the cholesterin in the serum could be discovered.

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[4] Grigaut, A.: Sur le dosage de la cholestérine dans les tissus, Compt. rend. Soc. de Biol., 1911, lxxi, 441.

[5] Weston, P., and Kent, G.: Determination of the Cholesterol Content of Human Serum by the Colorimeteric Method, Jour. Med. Research, 1912, xxvi, 531.

THE AMOUNT OF CHOLESTERIN IN NORMAL BLOOD

The amounts of cholesterin in normal blood-serum found by various observers who have used methods similar to the preceding, have been fairly concordant. Thus Grigaut placed the normal limit from about 1.2 to 1.8 gm. per liter of blood-serum, Weston and Kent[5] found from 1.17 to 2.97 with an average of 1.82 gm., Henes[6] found from 1.4 to 1.8 gm. per liter of blood-serum, and Widal, Weill and Laudat[7] found 1.74 and 1.95 in two normal fasting individuals. Iscovesco[8] has described a more elaborate extraction method, which apparently yields somewhat larger quantities than the above.[9] As will be seen from Table 1, the cholesterin in normal blood-serum as estimated by the method which we used, varied between 1.20 and 1.75 gm. per liter. Amounts of 2.0 gm. per liter or over may be regarded as definitely pathological. When those with marked thickening of the peripheral arteries and high blood-pressure were excluded from consideration, the age of the individual did not influence the amount of cholesterin in the serum. This is of interest in view of the fact that Wacker[10] observed an increase in the cholesterin content of the reserve fat of aged persons, and Robertson and Burnett[11] have advanced the view that an accumulation of cholesterin in the body may account for the well-known incidence of carcinoma with advancing age.

TABLE 1.—Cholesterin in Normal Blood-Sera

Age	Observations	Amount in Gm. per Liter
10-19	1	1.40
20-29	5	1.60-1.27-1.75-1.45-1.50
30-39	3	1.65-1.25-1.35
40-49	1	1.20
50-59	3	1.45-1.55-1.20
60-69	4	1.30-1.20-1.30-1.35

The cholesterin of the blood is not distributed evenly between the plasma or serum on the one hand and the red corpuscles on the other. Iscovesco[12] found varying relations between the two. Henes[6] found that on the average 54.5 per cent. of the blood cholesterin was present in the serum and 45.5 per cent. was in the corpuscles, so that when the serum was used for determinations the results were higher than when the whole blood was used. Grigaut and L'Huillier[13] obtained similar results in normal individuals, but they found that in pathological conditions the amounts in red blood-corpuscles remained fairly constant, even when the amounts in the blood-serum varied widely. For this reason the blood-serum is, as a rule, a more sensitive indicator of pathological changes than is the whole blood, and we have, therefore, made all of our determinations with blood-serum.

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[6] Henes, E.: Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei inneren Erkrankungen, Deutsch. Arch. klin. Med., 1913, cxi, 122.

[7] Widal, Weill and Laudat: La lipémie des brightiques, Semaine méd., 1912, xxxii, 529.

[8] Iscovesco, H.: Compt. rend. Soc. de Biol., 1912, lxxii, 257.

[9] Defaye: La cholestérémie, Etudes cliniques, Univ. de Bordeaux, No. 126, 1911-1912. Quoted by Henes.

[10] Wacker, L.: Ztschr. f. physiol. Chem., 1912, lxxx, 383.

[11] Robertson and Burnett: Preliminary Communication on the Part Played by Cholesterol in Determining the Incidence of Carcinoma, Proc. Soc. Exper. Biol. and Med., 1913, x, 140.

[12] Iscovesco, H.: Les lipoides du san: Dosage comparatifs des lipoides des globules frais et de sérum. Compt. rend. Soc. de Biol., 1912, lxxii, 985.

A number of authors have studied the effect of cholesterin ingestion on the cholesterin content of the blood. While some have failed to observe any relation between diet and cholesterinemia or between the amount of cholesterin taken by mouth and the amount in the blood, a number of recent workers have confirmed the opinion of those who have held that the cholesterin of the body is derived, in part at least, from the cholesterin in the food.[14] Thus Grigaut and L'Huillier[15] were able to raise the cholesterin content of a dog's blood from 1.8 to 3.0 gm. per liter by feeding 1 gm. of cholesterin a day, and in another animal the content was raised from 1.8 to 3.8 by feeding 2 gm. of cholesterin a day. After the feeding was discontinued the amounts of cholesterin in the blood-serum returned to normal rather rapidly. Similar observations with similar results have been made on man by Widal, Weill and Laudat, by Henes and by Lemoine and Gérard.[16] The cholesterin content of the blood may be raised either by feeding pure cholesterin or by giving a diet rich in this substance.

PATHOLOGICAL VARIATIONS IN THE CHOLESTERIN CONTENT OF THE BLOOD

It has long been known that the serum of certain patients is milky instead of being clear. These lactescent serums are in general associated with increases in the amounts of lipoid substances in the blood as determined by chemical methods, and in general also with hypercholesterinemia. Widal, Weill and Laudat[7] have shown, however, that the lipoids may be increased even though the serum is not milky and that no close parallelism exists between the degree of lactescence and the amounts of lipoids determined chemically.

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[13] Grigaut and L'Huillier: Taux comparé de la cholestérine des hématies et du sérum dans le sang normal et pathologique. Compt. rend. Soc. de Biol., 1912, lxxiii, 202.

[14] Doree, Gardner, Fraser, Ellis: Origin and Destiny of Cholesterol in the Animal Organism; a series of papers in the Proc. Royal Soc., 1908 to 1912.

[15] Grigaut and L'Huillier: Hypercholesterinémie d'origine alimentaire chez le chien, Compt. rend. Soc. de Biol., 1912, lxxiii, 304.

[16] Lemoine, G., and Gérard: Variations du taux de la cholestérine par rapport a l'alimentation, Bull. et mém. Soc. méd. d. hôp., 1912, 931.

Hypercholesterinemia has been frequently encountered in diabetes. Grigaut and Chauffard mention such an increase frequently. Bürger and Beumer[17] found an increase in four out of five diabetics, three of whom had milky serums. Henes found an increase in two out of seven patients. Apert, Pechry and Rouillard[18] were unable to find any definite increase in most of the diabetics whom they examined.

Our own observations on patients with diabetes are shown in Table 2. It will be seen that pathological increases of the cholesterin were present in six of ten patients, and that the largest amount occurred in a patient with diabetic coma. In two of the patients the cholesterinemia was increased after the sugar had been removed from the urine by placing the patients on a standard Von Noorden carbohydrate-free diet. Whether this rise was due to an increased amount of cholesterin in the diet or to an increased mobilization of lipoids already in the body, I am unable to say.

TABLE 2.—CHOLESTERINEMIA IN DIABETES

Name	Age	Blood-pressure	Sugar in urine	Cholesterin in gm. per liter	Remarks
Str.	20	120	7.0%	3.2	Severe case.
Bri.	56	145	4.5%	4.15	Coma. Mastoiditis.
LaF.	39	130	+ 0	2.8 3.3	Diabetic gangrene.
Wil.	63	175	+	2.25	Arteriosclerosis.
McB.	53	135	+ 0	1.7 1.9	Mild case.
Wic.	38	130	6.8%	2.8	Severe case.
Fee.	8	110	++	3.	Severe case.
Dib.	58	135	+	1.3	Very mild case.
Bar.	40	140	+	1.75	Very mild case.
Hil.	30	?	+	1.8	Mild case.

In jaundice due to an obstruction of the common bile duct there is uniformly present a hypercholesterinemia. Chauffard, LaRoche and Grigaut[19] have ligated the common bile duct in the dog and have found that the amounts of cholesterin in the serum rose from the normal of 1.75 gm. to amounts which varied between 2.4 and 5.4 gm. per liter. These same authors[20] have shown that hypercholesterinemia may also result from a clinical obstruction of the common bile duct, whereas in hemolytic jaundice the amount of cholesterin in the blood-serum is not increased. In five patients with obstructive jaundice whom we have studied there were definite increases in the amount of cholesterin in the blood. It seems evident, therefore, that common duct obstruction will lead to an increased amount of cholesterin in the circulation. Whether this is dependent entirely on a resorption of the bile or whether it is due in part to an associated disease of the liver, does not seem to be established at the present time.

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[17] Bürger, M., and Beumer: Zur Lipoidchemie des Blutes, Berl. klin. Wchnschr., 1913, xx, 112.

[18] Apert, Péchery, and Rouillard: Mesure de la cholestérinémie chez les diabétiques, Compt. rend. Soc. de Biol., 1912, lxxii, 822.

[19] Chauffard, Laroche and Grigaut: Recherches expérimentales sur la cholestérinémie après ligature du cholédoque, Compt. rend. Soc. de Biol., 1913, lxxiv, 1093.

[20] Chauffard, Laroche and Crigaut: Le taux de la cholestérinémie chez les hépatiques, Compt. rend. Soc. de Biol., lxx, 1911, 20.

TABLE 3.—Cholesterinemia in Jaundice

Name	Cholesterin in gm. per liter	Diagnosis
Wo.	3.50	Infectious (or catarrhal) jaundice.
Gr.	2.95	Common duct stone with jaundice.
Ch.	2.85	Common duct stone with jaundice.
Sh.	3.80	Malignant obstruction of the common duct.
Tri.	3.90	Malignant obstruction of the common duct.

Hypercholesterinemia occurs with frequency in patients with chronic Bright's disease, high blood-pressure and related conditions.[21, 7] I have devoted considerable attention to this group of cases with the hope that some relation might become evident between the hypercholestrinemia and the individual manifestations of cardiorenal disease. Our results which are shown in Table 4 have been arranged in the following order: the first four patients showed marked thickening of the peripheral arteries, but had no increase in blood-pressure and no albumin in the urine. The cholesterinemias in these patients were 2.25, 2.3, 1.80 and 1.95, respectively. The next group of patients showed chronic arterial hypertension without albumin in the urine. In this group the cholesterinemias were 2.0, 2.37, 1.95, 2.75, 1.85, 1.25, 3.2 and 3.3 gm. per liter. The third group includes those with chronic hypertension and albumin in the urine, but with good functional tests of the kidneys. In this group of patients, the figures were 2.0, 5.3, 3.85, 3.85, 1.25, 2.15, 1.75, 2.1, 2.25, 2.97. The final group includes those who showed more or less renal insufficiency as judged by the phenolsulphonephthalein test and an increase of hypobromite "urea" in the blood. They are arranged according to the degree of renal insufficiency, the more severe ones being placed last. The cholesterinemias in this group of patients were 3.5, 4.0, 1.35, 1.95, 1.85, 1.6, 1.73, 0.85, 0.8. In the first three of the preceding groups a hypercholesterinemia of moderate grade was encountered in the majority of the patients. Some of the lower figures may possibly have been due to an associated edema. It is interesting that we should have found an increase in the amount of cholesterin in two of four patients selected on account of a marked thickening of the peripheral arteries who

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[21] 21. Chauffard, Laroche and Grigaut: Le taux de la cholestérinémie au cours des cardiopathies chroniques et des nephrites chroniques, Compt. rend. Soc. de Biol., lxx, 1911, 108.

TABLE 4.—CHOLESTERINEMIA IN VASCULAR AND RENAL DISEASE

	Age	Blood-pressure	Urine	Peripheral Arteriosclerosis	Cholesterin in gm. per liter	Phthalein output	Hypobromite "Urea"
				GROUP I			
	59	145	neg.	marked	2.25	....	....
	49	154	neg.	marked	2.30	71.2	.25
	67	120	neg.	marked	1.95	....	....
	75	120	neg.	marked	1.80	....	....
				GROUP II			
	..	170	neg.	marked	2.00	75.0	.22
	68	180	neg.	marked	2.37	....	....
	53	180					
		210	neg.	marked	1.95	63.3	.31
	73	190	neg.	marked	2.75	....	....
	77	240	neg.	marked	1.85	....	....
	56	210	neg.	marked	1.25	48.8	.59
					....	28.0	....
	59	210	neg.	?	3.2	60.5	.65
	49	180	neg.	neg.	3.33	35.9	.44
					....	59.	....
				GROUP III			
	38	210					
		130	Hy.	mod.	2.0	72.	.36
	43	230	casts				
		230	Alb. and casts	slight	5.3	40.	.48
	39	210	Alb. and casts	slight	3.85	....	.51
	46	212	Alb. and casts	marked	3.85	77.5	.31
	47	230	Alb. and casts	marked	1.25	60.0	.46
	65	205	Alb. and casts	marked	2.15	....	.5
	58	170	Alb. and casts	marked	1.75	42.2	.38
	52	...	Alb. and casts	marked	2.10	74.7	.65
	45	235	Alb. and casts	Mod.	2.25	....	....
	44	265	Alb. and casts	......	1.97	....	...
				GROUP IV			
	48	172	Alb. and casts	Neg.	3.5	26.2	.34
	26	250					
		230	Alb. and casts	Neg.	4.0	34.0	.71
	54	190	Alb. and casts	Mod.	1.35	23.9	.53
	47	204	Alb. and casts	marked	1.95	22.3	.80
	58	225	Alb. and casts	marked	1.85	12.	1.55
	48	170	Alb. and casts	Mod.	1.45	....	...
					1.6	....	....
					2.1	....	....
	45	245	Alb. and casts	marked	1.73	6.8	2.02
	40	105	Alb. and casts	Mod.	.85	.0	4.39
psia	...	...	Alb. and casts	....	.08	....	....

showed no evident signs of kidney disease; for Chauffard[22] and Henes[6] found no definite relation between arteriosclerosis and cholesterinemia. In patients with high blood-pressure but without albumin in the urine and without other signs of nephritis, hypercholesterinemia is also common. Of the first three groups, the hypercholesterinemia is most marked in the third in which the high blood-pressure was associated with evident renal disease. The study of Group IV shows that when there is marked renal insufficiency, as measured by the phthalein test and by the accumulation of hypobromite "urea" in the blood, the cholesterin content of the serum tends to fall and may even become subnormal. Similar observations have been made by others,[21] and Widal, Weill and Laudat[7] stated that they were able to follow three patients in whom a fall of the cholesterin in the blood coincided with a rise of the incoagulable nitrogen. It seems evident from these observations that a hypercholesterinemia cannot be regarded as an index of renal insufficiency, for it may be present in cases without manifest renal disease, and it usually falls at the time of maximum retention of the urinary products. So far as our observations go, it would seem that a hypercholesterinemia may be associated with the degenerative processes in the blood-vessels without manifest renal disease.

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[22] Chauffard, A.: Les dépots locaux de cholestérine et leur rapports avec cholestérinémie, Rev. de med., 1911, xxxi, 176.

Chauffard and his school have studied the amounts of cholesterin in the blood during acute and chronic infections, and they have found that whereas in febrile tuberculosis the amount of blood cholesterin is diminished,[23] in typhoid fever it tends to be increased during the later stage of the disease.[24] They have also shown that in the later stages of pregnancy there is an increased cholesterinemia.[25] I have made no special study of these conditions, but have determined the cholesterin content of the blood in various conditions selected at random. Of these I wish to mention especially the case of a young girl with multiple tumors in the subcutaneous tissues which clinically resembled neurofibromas who had 5.63 gm. of cholesterin per liter of blood-serum. Unfortunately, it was not possible to remove one of the tumors for microscopic examination.

THE RELATION OF CHOLESTERINEMIA TO LOCAL CHOLESTERIN DEPOSITS

It has been mentioned that in certain pathological conditions there are abnormal deposits of cholesterin in the body, and the question arises as to the relation which may exist between such deposits and an increased cholesterin content of the blood. It is conceivable, for example, that the local deposits may depend entirely on local conditions which either favor a deposit of cholesterin from normal body fluids or which may possibly lead to a local production of cholesterin. The cholesterin deposits in infarcted areas and in tuberculous caseous material seem to be due to such local changes; and it has been shown[23] that in tuberculosis the cholesterin of the blood is normal or diminished. On the other hand, the cholesterin deposits may be regularly associated with such marked degrees of hypercholesterinemia as to favor the view that they result in large part from a surcharging of the blood with this substance. In such cases they may well be compared with the tophi of gout and one may speak of a cholesterin diathesis. Multiple tuberous xanthomas have been shown to be associated with marked local deposits of cholesterin,[26] and they are known to occur especially in association with general conditions, such as diabetes and jaundice, in which marked degrees of hypercholesterinemia are apt to be present. Furthermore, they have been shown to be associated with high degrees of cholesterinemia,[27, 28] so that they seem to depend on a surcharging of the blood with this substance. According to Chauffard and Laroche,[29] a similar relation exists for the more common xanthelasmas of the eyelids which are frequently encountered in chronic jaundice, and in two of four cases these authors demonstrated that xanthelasmas were associated with hypercholesterinemia. Greater interest attaches itself to the relation which exists between hypercholesterinemia and the cholesterin deposits in the blood-vessels, the retinae and the arcus senilis corneae which are so often associated with diseases of the kidneys and of the arteries. We know that hypercholesterinemia is frequent in such patients, and one is tempted to attribute these degenerations in part at least to the hypercholesterinemia present,[30] and especially so as Anitschkou[31] has shown that experimentally one may produce similar changes in the arteries by the administration of cholesterin. On the other hand, the cholesterinemia is by no means constant in these patients, and when present it is usually of moderate degree. Should one assume, therefore, that the cholesterin deposits were secondary to changes in the blood, one must postulate that there had been times of greater cholesterinemia during which the deposits occurred. The proof of such an assumption is not easily furnished and at present it seems more plausible to assume that these cholesterin deposits occurred secondary to degenerative changes in the tissues. Nevertheless the frequent occurrence of hypercholesterinemia in such patients and the experimental work of Anitschkou has opened up the whole subject of the relation of arteriosclerosis to hypercholesterinemia and a solution of this question is all the more urgent for the reason that should there be any relation between hypercholesterinemia and arteriosclerosis it would lead to an endeavor to control the cholesterin content of the blood as a prophylactic measure in the prevention of arterial degeneration.

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[23] Chauffard, Richet and Grigaut: La cholestérinémie au cours de la tuberculose pulmonaire, Compt. rend. Soc. de Biol., 1911, lxx, 276.

[24] Chauffard, Laroche and Grigaut: Évolution de la cholestérinémie chez les typhiques, Compt. rend. Soc. de Biol., 1911, lxx, 70.

[25] Chauffard, Laroche and Grigaut: Evolution de la cholestérinémie au cours de l'état gravidique et puerpéral, Compt. rend. Soc. de Biol., 1911, lxx, 536.

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[26] Pollitzer, S., and Wile, U. J.: Xanthoma tuberosum multiplex, Jour. Cut. Dis., May, 1912.

[27] Thibierge and Wiessenbach: Xanthome tubéreux disséminé et généralisé avec hypercholestéinémie, Bull. et mem. Soc. méd. d. hôp., 1911, xxxi, 93.

[28] Legendre, Joltrain and Levy-Franckel: Xanthome disséminé et généralisé avec chéloides secondaires. Bull. et mem. Soc. méd. d. hôp., 1912, xxxiv, 539.

[29] Chauffard and Laroche: Pathogénie du xanthélasma, Semaine méd., 1910, xxx, 241.

[30] Lemoine, G.: Théorie de l'artério-sclérose basée sur la cholestérinémie, Bull. et mém. Soc. méd. d. hôp., 1912, xxxiii, 227.

[31] Anitschkou: Die pathologischen Veränderungen innerer Organe bei experimentellen Cholesterinesterverfettung, Deutsch. med. Wchnschr., 1913, xxxix, 751.

CONCLUSIONS

By the method which we have used, the cholesterin in the blood of normal individuals is found to vary within rather narrow limits. It was definitely increased in obstructive jaundice, in six of ten patients with diabetes, and most patients with marked thickening of the peripheral arteries, chronic arterial hypertension and chronic nephritis. When, however, there is a marked functional insufficiency of the kidney, the cholesterinemia may fall to normal or even below normal. In a patient with multiple subcutaneous tumors (neurofibromas?) there was a marked hypercholesterinemia. Excepting in the case of obstructive jaundice, where the cause of the hypercholesterinemia is in part at least due to a resorption of bile, little is known about the etiology of pathological increases in the amount of cholesterin in the blood.

THE UREA CONTENT OF THE SPINAL FLUID WITH SPECIAL REFERENCE TO ITS DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE

A SERIES OF NINETY-SEVEN CASES *

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In a study of the literature concerning the urea content of the spinal fluid, we have been struck by the amount of work done on this subject by French clinicians as contrasted with its apparent neglect by German, English and American clinicians.

The normal quantity of urea in the spinal fluid, as indicated from a review of a considerable mass of material in the literature, varies between 0.01 per cent. and 0.05 per cent. Mollard and Froment,[1] in 1909, reviewed the literature up to that time and cited the works which follow in brief. Richet, in 1897, gave twenty-five analyses and stated "possibly urea." Deniges and Sabrazès, and Sabrazès and Binaud,[2] in 1895, reported two cases of tuberculous meningitis showing 0.015 per cent. and 0.035 per cent. of urea in the spinal fluid. Comba,[3] in 1899, reported two cases of acute uremia, in which there was an increase in the total nitrogen of the spinal fluid. Dirksen,[4] in 1900, reported four cases, one of uremia in which the urea content was 0.04 per cent., while three cases in which there was no uremia showed 0.01 to 0.015 per cent. Carrière,[5] in 1905, stated that he had found the normal amount of urea to be 0.01 to 0.015 per cent. Emery[6] gave the normal as 0.035 to 0.04 per cent., Widal and Froin[7] as varying between 0.015 and 0.035 per cent., Castaigne and Weil[8] from 0 to 0.15 per cent., Graham Forbes[9] as 0.035 to 0.04 per

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[1] Mollard and Froment: Urée dans le liquide cephalorachidien et urémie Nerveuse, Jour. de Physiol. et de Path. Gen., 1909, ii, 263.

[2] Sabrazès and Binaud: Traité de pathologie Générale de Bouchard 1897, vi, 650.

[3] Comba: Clin. Med. Ital., 1899, No. 9, p. 555.

[4] Dirksen: Etude sur la composition chemique et la concentration moleculaire du liquide céphalorachidien, Thèse de Paris, 1900 to 1901.

[5] Carrière: Etudes sur le liquide céphalorachidien dans l'urémie nerveuse, Séances et memores de la Soc. de Biol., 1905, p. 239.

[6] Emery: Clinical Bacteriology and Hematology, Blakiston Sons & Co., 1912.

[7] Widal et Froin: L'urée dans le liquide céphalorachidien de Brightiques. Gaz. d hôp., Oct. 25, 1904, p. 1182.

[8] Castaigne and Weill: Considerations pratiques d'order clinique et therapeutique sur le liquide céphalorachidien des urémiques., Jour. méd. franç., 1911, v, 34.

[9] Forbes: Pathology of the Cerebrospinal Fluid. Lavori e reviste di chimicae microscopia clinica, October, 1908, p. 33.

cent. Finally, Mollard and Froment asserted that normally the quantity of urea in the spinal fluid was negligible, but in Bright's disease it might increase to a point of diagnostic or prognostic significance. From the study of twenty-three cases collected at that time they concluded (a) that a notable increase of urea in the spinal fluid could not be considered as pathognomonic of uremia with involvement of the nervous system, since it might be found whenever the kidneys functionated improperly; (b) that a urea content attaining or exceeding 0.4 per cent. meant a pure uremia and foretold a rapidly approaching fatal outcome; (c) that a urea content below 0.4 per cent. did not permit of definite conclusions, but should be considered in conjunction with concomitant symptoms.

In 1910, Froment[10] reviewed the literature, included the report of cases in his preceding article with Mollard, and collected reports of thirty-four new cases, making in all fifty-seven cases reported up to 1910.

From the study of these cases, Froment drew the following conclusions:

> That all pathological conditions without kidney involvement showed a negligible quantity of urea in the spinal fluid, namely, 0 to 0.015 per cent. and that it never attained 0.1 per cent., while in nervous uremia the content varied between 0.15 and 0.45 per cent.; that some cases without a definite picture of uremia showed a definite increase of urea, as for instance 0.25 per cent. to 0.29 per cent. in cases of arteriosclerosis or Bright's disease in which at necropsy there were found multiple cerebral softenings, cerebral hemorrhages or meningitis; that one could determine the association of retained urea and uremia even though other pathological states existed; that with a spinal-fluid urea attaining or exceeding 0.4 per cent. one could definitely say that a pure, or more rarely, an associated uremia existed and foretell a nearing fatal outcome. With less than 0.1 per cent. of urea the diagnosis of uremia should be rejected. If the urea content of the spinal fluid lay between 0.1 per cent. and 0.3 per cent. the condition was frequently but not always to be interpreted as a pure uremia while one could not reject all other diagnoses. Should there be uremia the prognosis was often favorable.

Since our series of ninety-seven cases is practically limited to spinal fluids, we have so far said nothing as to the urea content of blood. While the urea content of spinal fluid was being studied and reported that of the blood and body fluids was being concurrently investigated. In almost all cases the urea content of all these fluids was found to agree. There were occasional discrepancies, but these were largely to be explained by variations in the time of obtaining the fluid and in the methods of examination. All observers tend to the conclusion that the quantity of urea is practically the same in all body fluids under similar circumstances. In 1906, Javal and Adler[11] reported four cases with determinations of the urea content of more than one body fluid, all tending to establish an accord. In 1910, Javal and Boyet[12] reported the examination of the body fluids in ten cases with practically an agreement throughout. Several authors reported isolated cases in which the urea content of blood and spinal fluid was about the same. It remained for Javal[13] to establish this fact. This he did as the following study will show. In all cases the different fluids were obtained at the same time and the urea content considered as that part of the total nitrogen decomposable by sodium hypobromite.

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[10] Froment: Diagnostic et prognostic de l'urémie nerveuse par le dosage de l'uree dans le liquide céphalorachidien, Lyon méd., 1910, i, cxiv, 269.

[11] Javal and Adler: La diffusion de l'urée dans les transudats de l'organisme. Application au diagnostic et au prognostic de l'urémie, Séances et Mém. de la Soc. de biol., 1906, lxi, 235.

The estimation of urea was made on blood and spinal fluid in eighteen cases, on blood and edema fluid in four cases, on pleural fluid and edema fluid in two cases, on ascitic fluid and edema fluid in one case, on blood and pleural fluid in five cases, on pleural fluid and spinal fluid in three cases. In all of these the urea content was practically identical, the variation being negligible, usually about 0.005 per cent., occasionally 0.01 per cent. Javal himself regarded the uniformity as established.

Accepting this fact, Castaigne and Weill[8] state that inferences may be drawn from examination of the spinal fluid which will be identical with those drawn from examination of the urea content of blood. They also report four cases in which uremia terminated fatally and in which the spinal fluid urea varied from 0.115 per cent. to 0.767 per cent.; and twelve cases in which uremia terminated in recovery, temporary at least, in which the spinal fluid urea was 0.1 per cent. to 0.2 per cent. Finally, they state that the urea content never reaches 0.1 per cent. in normal states while in established uremia it may vary from 0.1 per cent. to 0.5 per cent., or even higher.

From the work of Widal[14] and further work of Javal[15] on the parallelism in the urea content of different body fluids, the variations in the urea of the spinal fluid assume an importance equal to that of the blood urea. Widal states that, with a blood urea content of more than 0.05 per cent., there is some retention, and that one can follow at times the gradual increase from 0.06 per cent. to 0.07 per cent., and so on upward. He regards a quantity of urea below 0.2 per cent. as justifying a prognosis for life of more than one year; a quantity between 0.2 per cent. and 0.3

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[12] Javal and Boyet: La Retention de l'uree et sa diffusion dans les liquides de l'organisme, Séances et Mém. de la Soc. de Biol., 1910, lxviii, 527.

[13] Javal: Contribution Numérique à l'étude de la composition clinique de sérosités physiologiques et pathologiques de l'organisme chez l'homme, Jour. de phys. et de path. gén., 1911, p. 508.

[14] Widal: Le prognostic dans le mal le Bright par le dosage de l'urée du sang. Les rémissions temporaires et trompeuses de l'azotèmie, Bull. et Mem. de la Soc. de Hôp. de Paris, 1911, xxxii, 627.

[15] Javal: Le grande azotémie, ses formes, son evolution son prognostique etudies par le dosage méthodique de l'urée dans le sang et dans les serosités de l'organisme, Bull. et Mém. de la Soc. de Hôp. de Paris, 1911, xxxii, 485.

per cent. as indicating a survival of only weeks or months, and a quantity above 0.3 per cent. as indicating a not far distant fatal outcome. He cites eighteen cases in which the blood content of urea was 0.2 per cent. to 0.3 per cent. of urea. The longest survival was seven months, while thirteen patients died within two months. Of thirteen cases with a quantity above 0.3 per cent., all died within one month.

Javal, too, agrees with Widal that with a blood urea content above 0.2 per cent. the fatal outcome is a question of weeks or months. Of his twenty-one cases, the one that survived longest lived but twenty-one months. In agreement with Widal he cites cases with marked remissions, but always with an eventual fatal outcome.

In the year 1912, several authors reported the urea content of the spinal fluid in infants and children. Nobécourt and Darré[16] reported twelve cases, in all of which there was evidence of nephritis. Of five cases in which there was either simple albuminous nephritis or the type associated with retained chlorids, the urea of the spinal fluid was well within normal limits. In four cases conforming to the type of combined urea and chlorid retention, the minimum urea content of the spinal fluid was 0.044 per cent., and the maximum 0.083 per cent. In a third class, comprising three cases, the lowest figure on admission to the hospital was 0.123 per cent., and the highest 0.204 per cent. These three patients left the hospital greatly improved with the spinal fluid urea within the normal limits. The subsequent course of the disease in these patients was not known.

Nobécourt, Bidot and Maillet[17] report twelve examinations of the spinal fluid in infants. They concluded from these that a urea content above 0.1 per cent. is, as a rule, soon followed by death. Six infants in their series had over 0.1 per cent. and less than 0.2 per cent. of urea in the spinal fluid. The longest duration of life among the six infants was twenty-nine days. The urea content of the spinal fluid in three of the series was above 0.2 per cent., and the longest duration of life among these patients was three days.

Nobécourt, Sevestre and Bidot[18] reported fourteen new examinations of the spinal fluid in infants under one year of age. Five of these showed urea content of 0.04 per cent. to 0.06 per cent., all without apparent kidney lesions, with the exception of one (0.057 per cent. urea), which showed at necropsy lesions of the kidney epithelium and a little thicken-

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[16] Nobécourt and Darré: L'urée du liquide céphalorachidien dans les nephrites de l'enfance, Bull. et mém. Soc. de hôp. de Paris, January, 1912, p. 16.

[17] Nobécourt Bidot and Maillet: Valeur prognostique de l'élévation du taux de l'urée dans le liquide céphalorachidienne des nourrissons, Bull. et Mém. de la Soc. de Hôp. de Paris, July, 1912, p. 47.

[18] Nobécourt Sevestre and Bidot: L'urée dans le liquide céphalorachidien des nourrissons, Arch. de méd. des Enf., November, 1912, p. 826.

TABLE 1.—Pathological Conditions, Nephritis Clinically Excluded

ase o.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
1	33	0.02	Cerebral tumor. Death.	....	Differential: Polymorphs, 15%; lymphocytes, 85%.
2	11/12	0.05	Tuberculous meningitis.	....	Fluid bloody. One examination. No tubercle bacilli found.
3	3	0.027	Acute anterior poliomyelitis.	Paralysis of face, weakness of legs. Improvement.	Cells per c.mm., 5 Butyric acid test neg. Polys., 2%; lymphos., 98%.
4	37	0.053	Acute general tuberculosis.	....	25 c.c. bloody fluid.
5	3	0.044	Tuberculous meningitis.	....	12 c.c. clear fluid. Polymorphs. 3%; lymphos., 71%; endoth., 26%; NaCl, 0.642%.
6	3	0.083	Tuberculous meningitis.	....	Lymphocytes, 100%. 10 c.c. clear fluid. Tubercle bacilli present.
7	3	0.029	Tuberculous meningitis.	....	Tubercle bacilli present.
8	11	0.04	Pneumococcus meningitis.	....	Pneumococci present.
9	18	0.033	Tuberculous meningitis.	....	Tubercle bacilli present.
0	29	0.08	Syphilitic meningitis.	Wassermann positive in both blood and spinal fluid.	Differential: Lymphos., 94%. Butyric acid test positive.
1	8/12	0.043	Lobar pneumonia with convulsions.	....	Butyric acid test negative. NaCl, 0.747%. Cultures sterile.
2	7/12	0.058	Pneumococcus meningitis.	Necropsy. No kidney involvement.	Pneumococcus present. NaCl, 66%.
3	13	0.053	Tuberculous meningitis.		
4	22	0.053	Suppurative meningitis. Mastoiditis.		
5	5½	0.04	Streptococcus meningitis. Mastoiditis.	....	Streptococcus present.
6	2½	0.033	Tuberculous meningitis.	....	Tubercle bacilli present.
7	11/12	0.022	Bronchopneumonia. Furunculosis.		
8	31	0.067	Meningococcus. Septicemia, infective endocarditis. Necropsy.		
9	41	0.033	Tuberculous meningitis.	....	Tubercle bacilli present.
20	22	0.049	Otitis media, acute.		
21	6	0.036	Suppurative meningitis.		
22	6/12	0.035	Tuberculous meningitis.	....	Tubercle bacilli present.
23	5	0.022	Catarrhal gastritis.	Convulsions, cause not determined.	
24	4	0.029	Acute general tuberculosis.	....	No cells.
25	35	0.071	Disseminated myelitis.	Slight albuminuria. Bloood-pressure 110.	
26	5	0.026	Tuberculous meningitis.	....	
27	22	0.049	Suppurative otitis media.	Albumin, faint trace, no casts.	

TABLE 1.—Pathological Conditions, Nephritis Clinically Excluded.—(Continued)

se o.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
28	15	0.053	Bronchopneumonia.	Albumin, faint trace, no casts.	Normal.
29	2½	0.053	Tuberculous meningitis.	Drowsiness to coma.	
30	19	0.053	Tuberculous meningitis.	Albumin, faint trace, no casts.	Tubercle bacilli present.
31	6	0.019	Tuberculous meningitis.	Stupor.	Lymphocytes, 99%. No tubercle bacilli found.
32	15	0.024	Tuberculous meningitis.	No albuminuria. No casts.	Lymphocytes, 91%.
33	34	0.053	Erysipelas.	Hysteria.	Lymphocytes, 91%.
34	53	0.025	Chronic alcoholism. Cerebral edema.	Delirium tremens. No albuminuria. No casts.	
35	46	0.053	Cerebral glioma.	Necropsy. Kidneys normal.	
36	38	0.026	Tertiary syphilis. Gumma of lenticular nucleus.	Necropsy. Kidneys normal.	
37	..	0.053	Tuberculous meningitis. Suppurative otitis media.	Faint trace albumin. No casts.	Tubercle bacilli present.
38	3¾	0.035	Tuberculous meningitis.	Albumin, faint trace, granular casts.	Lymphocytes, 67%.
39	11	0.014 0.038	Cerebral tumor.	Operation. Trace albumin. No casts.	
40	31	0.053	Lobar pneumonia. Alcoholic delirium. Tuberculous meningitis.	Trace albumin.	Tubercle bacilli present.
41	7	0.01	Tuberculous meningitis.	....	Tubercle bacilli present.
42	36	0.053	Bulbar palsy. Tertiary syphilis.	No kidney symptoms.	
43	48	0.059	Suppurative meningitis. Suppurative otitis media.	No renal symptoms.	Pneumococci present.
44	16	0.010	Acute tonsillitis. Chr. valvular cardiac disease.	Trace albumin, few hyaline casts.	
45	1	0.038 0.04 0.045 0.07	Chronic basilar meningitis.	Necropsy. No renal lesion.	
46	38	0.135	Acute general tuberculosis. Tubercular meningitis.	Necropsy showed only a few miliary tubercles of kidney. Some congestion of glomeruli and slight degeneration of tubular epithelium.	Tubercle bacilli present.
47	8	0.179	Tuberculous meningitis.	Duration two weeks. Delirium. Coma. Fundi show some congestion of discs. No albuminuria. No casts.	Tubercle bacilli present. Lymphocytes, 76%.
48	53	0.03	Locomotor ataxia.	....	Wassermann positive.
49	26	0.018	Chronic pulmonary tuberculosis.		

TABLE I.—Pathological Conditions, Nephritis Clinically Excluded.—(Continued)

Case No.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
50	40	0.115	Paresis.	Very slight albuminuria. Casts in one of three examinations. Blood-pressure 140. Eye-grounds normal. No nephritic history, no signs.	Wassermann positive.
51	2½	0.053	Enterocolitis.		
52	12	0.035	Chronic pulmonary tuberculosis.	Urine normal.	
53	8/12	0.041	Acute general tuberculosis.	Urine normal.	
54	3½	0.026	Acute general miliary tuberculosis.	....	Tubercle bacilli present.
55	18	0.029	Fracture base of skull. Suppurative meningitis.		
56	21	0.167	Perithelioma of spinal cord.	No abnormalities of urine. No evidence of nephritis. Diagnosis by operation.	

ing of the connective tissue. One case showed 0.17 per cent. and 0.23 per cent. of urea in the spinal fluid on successive examinations. At necropsy there was some thickening of the connective tissue of the capsule and its capillaries. The liver, on the other hand, showed marked fatty infiltration and some degeneration. There was one case which exhibited signs of meningitis that were followed by gastro-intestinal disturbances. The last case showed, in two examinations, 0.189 per cent. and 0.377 per cent. of urea in the spinal fluid. Death occurred three days after the second lumbar puncture. No necropsy was made.

With all these facts in mind our own series of ninety-seven examinations has been to us most interesting.

Our method of estimating urea has been as follows: To 120 c.c. of a mixture of 40 parts of ether and 80 of alcohol, all the spinal fluid available was added and allowed to stand twenty-four hours in a glass-stoppered bottle. The mixture was then filtered through smooth filter-papers, the latter being moistened with absolute alcohol. The bottle was then carefully washed and the precipitate cleansed at least four times with hot absolute alcohol. The filtrate was evaporated to a syrupy consistency. The residue was then taken up once more with absolute alcohol, filtered and reevaported to a very little syrupy liquid. This was taken up in distilled water and put into a small vial in the hypobromite apparatus. One c.c. of nitrogen gas then equalled 0.002694 gm. of urea.

TABLE 2.—Uremia Resulting in Death

se o.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
1	47	0.120	Nephritis, chronic. Acute uremia. Death.	Albuminuric retinitis. Blood-pressure 240-300 mm. of mercury. No necropsy.	15 c.c. clear fluid. No cells.
2	45	0.062 Blood 0.07	Chr. interstitial neph. Acute uremia. General arteriosclerosis.	Albuminuric retinitis. albuminuria, casts, coma. No necropsy.	No cells. Butyric acid test negative.
3	32	0.436 Blood 0.365	Chr. interstitial neph. Acute uremia. Death.	Albuminuric retinitis. Convulsions. Blood-pressure 198 mm. Albuminuria, casts.	NaCl 0.802.
4	35	0.402 Blood 0.363	Chr. interstitial neph. Acute uremia.	Albuminuric retinitis. Blood-presure 180-230. Nausea, vomiting. Albuminuria, casts.	
5	43	0.571 Blood 0.624	Chr. interstitial neph. Acute uremia.	Albuminuric retinitis. Blood-pressure 204 to 220 of mercury. Necropsy.	No cells.
6	25	0.107	Chr. interstitial neph. Acute uremia. General arteriosclerosis.	Albuminuria and casts. Blood-pressure 170-240 of mercury.	
7	65	0.14	Chr. interstitial neph. Acute uremia.	Albuminuria and casts. Blood-pressure 199 mm.	
8	35	0.161	Chr. neph. Cardiac decompensation.	Albuminuria. Casts. Died cardiac death. Blood-presure 148-160.	
9	50	0.619	Chr. interstitial neph. General arteriosclerosis. Albuminuric retinitis. Uremia.	Albuminuria very slight. Occasional casts.	
0	40	0.311 Blood 0.343	Chr. interstitial neph. Acute uremia. Cardiac decompensation.	Blood-pressure 180 mm. of mercury.	Polymorphs., 99%.
1	35	0.402 Blood 0.303	Chr. neph. Uremia.	Albuminuria, casts. Nausea, vomiting. albuminuric retinitis.	
2	42	0.26	Chr. interstitial neph. Uremia. Cardiac decompensation.	General edema. Stupor. Necropsy.	
3	26	0.673 Blood 0.28	Chronic diffuse neph. Uremia.	Prolonged kidney history. Semi-coma. Anuria.	Polymorphs., 92%.
4	32	0.026	Chronic diffuse neph. Uremia.	Kidney history of two years. Edema, dyspnea, oliguria, headache, coma. Marked albuminuria.	
5	63	0.35 Blood 0.32	Chronic diffuse neph.	Headache, vomiting. oliguria, albuminuria. Coma.	

TABLE 2.—Uremia Resulting in Death.—(Continued)

ase No.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
16	31	0.087	Chronic parenchymatous nephritis.	Stupor. Albuminuric retinitis. Marked albuminuria. Many casts. Blood-pressure 195-225 mm.	Polymorphs., 83%. NaCl 0.77%.
17	27	0.525 Blood 0.538	Chr. interstitial neph. Acute uremia. Cardiac hypertrophy.	Blood-pressure 158-192. Marked albuminuria. Casts, convulsions, coma.	
18	42	0.177	Chr. interstitial neph. Cardiac hypertrophy. Uremia.	Headache. Systolic blood-pressure 185-235 mm. Albuminuric retinitis. Stupor.	
19	32	0.298 Blood 0.308	Chr. interstitial neph. Empyema. Frontal sinus.	Marked albuminuria. Many casts. Systolic blood-pressure 138-195 mm.	
20	33	0.33 Blood 0.49	Chr. interstitial neph.	Albuminuric retinitis.	
21	25	0.453 Blood 0.471	Chr. interstitial neph.	Convulsions. Retinal hemorrhages. Blood-pressure 178-190 mm.	

All the determinations were made by one of us (S. G.), using always the above method. The disagreements in the amounts of blood and spinal fluid urea that are occasionally reported, are probably due to the fact that the determinations were not made at the same time.

The cases, as may be seen from the tables, are arranged in four groups: (1) cases in which nephritis could be clinically excluded; (2) cases in which death was caused by uremia; (3) cases in which clinical nephritis did not terminate fatally, and (4) pathological conditions with a diagnosis other than uremia, from which, however, nephritis could not be excluded.

Of cases belonging to Group 1. in which nephritis could be excluded, there were fifty-six. Thirty-three of these cases showed less than 0.05 per cent. urea in the spinal fluid; fifteen cases 0.05 to 0.06 per cent.; four cases showed 0.067 per cent., 0.071 per cent., 0.08 per cent. and 0.083 per cent., respectively, with no satisfactory explanation, and four cases show, respectively, 0.135, 0.179, 0.115 and 0.107 per cent. In none of the last four was there sufficient ground to explain the high urea content.

In the second group, which comprises twenty-one cases in which uremia was present, the constant high percentage of urea in the spinal fluid was very striking. In thirteen cases it was above 0.2 per cent., in five cases between 0.1 per cent. and 0.2 per cent., and in three cases under 0.1 per cent. Two of the last three were, however, above normal.

In Group 3 there were eight non-fatal cases of nephritis. The two patients in this group (Nos. 1 and 2), who showed marked increase in the spinal fluid urea, left the hospital with little if any improvement. The history of these two cases in which there was high urea content was

TABLE 3.—NEPHRITIS NOT TERMINATING IN DEATH

Case No.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
1	49	0.22	Chronic uremia. Chr. interstitial nephritis. Gen'l arteriosclerosis.	Albuminuria, casts. Headache, vomiting. Unimproved.	25 c.c. clear, no cells. Butyric acid test negative.
2	37	0.193	Chr. interstitial neph. Albuminuric retinitis. Optic neuritis.	Headache, vomiting, unconsciousness, weakness. Slight albuminuria. Few hyaline casts. Blood. Improvement slight.	
3	55	0.035	Chr. interstitial neph. Acute uremia.	Moderate edema. Slight edema of retina. Albuminuria marked. Casts many. Blood-pressure 107-208. Greatly improved.	
4	24	0.025	Chr. interstitial neph.	History of very marked albuminuria two years previously. Headache for two years. Slight albuminuria. Occasional casts. Slight edema. Greatly improved. Eye-grounds normal.	
5	51	0.051	Chr. interstitial neph. Cardiac hypertrophy.	Blood-pressure 180-185. Marked albuminuria. Slight edema. No nervous symptoms. Greatly improved.	
6	35	0.025	Acute nephritis. Acute pharyngitis. Acute bronchitis. Uremia.	Edema of legs and chest, nausea, dyspnea, convulsions, fundi normal, many casts. Apparently cured.	
7	39	0.06 0.05	Chr. interstitial neph.	Headache, vomiting, neuroretinitis. Systolic blood-pressure 168-220. Moderate albuminuria, considerable number of casts. Temporarily improved.	
8	46	0.08	General diffuse neph. Arteriosclerosis. Staphylococcus aureus. Pyemia.	Death due to sepsis. Necropsy.	

TABLE 4.—Pathological Conditions with Diagnosis other than Uremia, from Which, However, Nephritis Cannot Be Excluded

Case No.	Age Years	Urea Pct. Spinal Fluid	Diagnosis Clinical	Affecting Diagnosis	Further Examination of Spinal Fluid
1	55	0.431	Cerebral hemorrhage. Diabetes mellitus.	Glycosuria. Acidosis. Urine shows heavy trace of albumin. No casts. Specific gravity 1.037.	Blood-tinged fluid. Polymorphs., 92%; lymphos., 8%.
2	35	0.07	General paresis.	Slight albuminuria. Casts. Blood. Wassermann strongly positive.	Wassermann strongly positive.
3	21	0.018	Nephritis (?) Neuroretinitis, both eyes. Myxedema (?)	Slight albuminuria. Occasional casts. Blood-pressure 100-110.	
4	38	0.048	Nephritis (?) Uremia (?)	Slight albuminuria. Many hyaline casts. No definite history.	22 c.c. clear fluid. Wassermann negative. Butyric acid test negative.
5	39	0.067	Dementia.	Convulsions. Hallucinations. Blood-pressure 110-130. Slight albuminuria. Casts in two of six examinations made.	Polymorphs., 35%; lymphocytes, 58%; large monos., 5%; eosinophils, 2%.
6	36	0.053	Old hemiplegia. Broken cardiac compensation. Uremia (?)	Albuminuria marked. Many hyaline and granular casts. Admitted moribund. Irrational. Temp 98 F. Eye-grounds normal.	Polymorphs, 98%.
7	2	0.358	Tuberculous meningitis.	Unconscious. Vomiting of two weeks' duration. No examination of urine. Blood-pressure not taken. Survived one day in hospital.	No tubercle bacilli found.
8	36	0.421	Acute general tuberculosis. Tuberculous meningitis.	Chronic alcoholism. Eye-grounds show only a blurring of discs. Slight albuminuria. No casts. Blood-pressure 110-120. Edema none. Septic temperature. Irrational.	No tubercle bacilli found.
9	37	0.153	Atrophy of optic nerves.	Headache, vomiting. Unconsciousness, three attacks. Slight albuminuria. No casts. Blood-pressure not taken.	
10	8/12	0.614	Tuberculous meningitis.	Duration six days. Vomiting, convulsions, coma. No Kernig. Some stiffness of neck. Slight dyspnea. No Babinski reaction.	No tubercle bacilli in three examinations of spinal fluid. First lymphocytes, 74%; second lymphocytes, 42%.
11	65	0.121	Chr. interstitial neph. ? Cardiac decompensation. Senility.	Trace of albumin in two of ten examinations. Hyaline casts in four examinations. No nervous symptoms.	
12	49	0.095	Diabetes mellitus. Ulcerative colitis. Chronic diffuse neph. General arteriosclerosis. Cardiac hypertrophy.	Albuminuric retinitis. Blood-pressure 197-220. Marked albuminuria.	

not subsequently followed, but in the light of experience the patients may be presumed to have survived only a short time.

Of the twelve cases tabulated under Group 4, cases 1, 7, 8 and 10 present interesting problems. Unfortunately, necropsies could not be obtained in any of them, and it is therefore impossible to exclude nephritis as a complication or indeed the principal cause of death, but we feel that the burden of proof lies with the clinician as regards diagnosis.

CONCLUSIONS

Our conclusions as to the interpretation which may safely be made from increased amounts of urea in the spinal fluid must remain, both diagnostically and prognostically, almost the same as those of the authors quoted.

1. A spinal fluid urea content higher than 0.2 per cent. indicates a severe uremia and a rapidly fatal termination.

2. A content between 0.1 per cent. and 0.2 per cent. means a rapidly fatal termination in the majority of cases of nephritis.

3. A content between 0.05 per cent. and 0.1 per cent. does not permit of any definite conclusions either as regards diagnosis or prognosis. Such a content is, however, suggestive of severe urea retention and must be taken into consideration in the diagnosis of the condition.

4. As to diagnosis we believe that the determination of the presence or absence of urea retention in the body fluids will go far to clear up certain difficult problems where the question of uremia enters into consideration.

We desire to express our thanks to the attending physicians and members of the house staff who have made this material available.

41 East Seventieth Street.

THE GONOCOCCUS COMPLEMENT-FIXATION TEST AND ANALYSIS OF RESULTS FROM ITS USE*

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In recognition of the recent admirable work by Schwartz and McNeil on the complement-fixation test in gonococcic infections, the fact must not be overlooked that Müller and Oppenheim, in 1906, were the first to apply this reaction to a gonorrheal affection and consequently are entitled to the distinction of being termed the originators. The present popularity of this test has been the outgrowth of the suggestion made by Schwartz and McNeil — namely, that of the employment of a polyvalent antigen. As a result of their labors, these workers contend, and seem to have proved conclusively, through animal experimentation: (1) "that the different strains of the gonococcus differ markedly one from another — so much so that the antibodies produced in the body by the toxin of one strain will in many instances not bind the complement in the presence of an antigen prepared from another strain. Therefore, if only one strain is used in the preparation of the antigen, a great many negative results would be obtained in positive cases; (2) an antigen prepared from many strains fixes the complement whenever one of its component strains does so, and consequently the necessity of testing a serum against a number of antigens separately is avoided. It is not to be denied that there probably are other strains of gonococci differing widely from any present in the polyvalent antigen, so that at times a negative result will be obtained in a positive case."

While we recognize the fact that a negative reaction may mean nothing, in fact, may be erroneously contradictory, the significance, on the other hand, of a positive reaction has been so great — more specific, in fact, than when the lipotropic antigen, commonly employed in the performance of the Wassermann reaction, is utilized — that we have applied the test for the past few months in a large series of diverse cases with the most gratifying results. Without entering on any discussion of the theories governing fixation or deviation of complement and hemolysis, it is our purpose, at this time, merely to outline our own technic, designating certain points of superiority which it may possibly possess over that employed by Schwartz and McNeil, and to submit the analysis and results of cases in which serums were subjected to the gonococcus complement-fixation test.

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DISCUSSION OF TECHNIC

The technic utilized and advocated by Schwartz and McNeil in the performance of the complement-fixation test for gonococcic infections embodies what may be termed the minimal quantity method. That is, the smallest quantities of the component substances entering into the reaction are employed that are compatible with practicability. Other than as a matter of economy and questionable conservation of time, this method possesses no recommendation. In fact, from a comparative study of the results in a series of cases in which Schwartz and McNeil's method is contrasted with the technic analogous to the Wassermann reaction as employed by us, it has appeared that the advantage has always rested with the latter or larger quantity method, in that the hemolytic readings seemed to be easier of interpretation.[1] Moreover, we have been impressed by the fact that the quantity of antigen employed in the former case, as will be seen presently, is too great — being indeed as much as, and more than, that utilized by us with five to ten times the gross quantity of material.

Schwartz's latest method and the technic which we practiced for a time in comparison with our own gonococcus complement-fixation test is as follows, so far as the quantities of the ingredients participating in the reaction are concerned: (1) patients' serum, 0.02 c.c.; (2) salt solution, sufficient to equalize the volume in each tube; (3) antigen (routinely 0.3 c.c. in one tube and 0.15 c.c. in another tube, of a commercial preparation diluted 1 to 10). These quantities are determined by preliminary standardization with a fresh known negative and a known positive serum; the positive showing the true antigenic dose, and the negative the highest quantity of antigen which will allow complete hemolysis; in the actual test this large quantity of antigen is placed in one tube and one-half the quantity in a second tube; (4) complement 0.1 c.c. of a dilution 1 to 10; (5) amboceptor, 0.1 c.c. representing twice the lowest quantity that will completely hemolyse 0.1 c.c. of the cell suspension with 0.1 c.c. of complement in one hour; (6) sheep's red blood-cells (5 per cent. suspension), 0.1 c.c. Incubation is made for one-half hour at 37 C.

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[1] If it be necessary or desirable to practice economy in the performance of the test, we would suggest, in preference to the very small quantities employed by Schwartz and McNeil, which are more or less tedious to manipulate, just half of the component materials as employed in our technic. We have resorted to this modification on several occasions with results just as satisfactory as those obtained by the regular method.

in a water-bath or for one hour in dry heat, before and after the addition of the hemolytic system.

The technic on which we have learned to place the greatest reliance is essentially that utilized by us in the performance of the Wassermann reaction, merely substituting the gonococcus specific antigen for the syphilitic lipotropic antigen, employing always the carefully standardized single complement unit and the routine standardization of antigen and amboceptor. Briefly, the steps in the daily procedure are as follows:

AUTHORS' TECHNIC

As previously stated, a detailed description of the fundamental serological principles involved in the complement-fixation or deviation reaction, will be omitted from this discussion. We shall submit, therefore, merely a table representing the routine procedure in the performance of the gonococcus complement-fixation test (Table 1).

We believe that the features of importance in the proper execution of this test are: the required inactivations, the exact standardization of the hemolytic amboceptor and suspension of sheep's red blood-corpuscles, and paramountly, the complement and antigen each time the reaction is undertaken.

ANTIGENS

The preparation of the various ingredients entering into the reaction will receive no consideration at this time—with one exception, namely, the antigen. This, however, is of such importance with respect to the gonococcus complement-fixation test that it must receive some discussion, since on the integrity and specificity of this antigen depends the whole value of the test in gonorrheal infections. The necessity of a polyvalent antigen is indisputable, presumably owing to the diversity of the strains of the gonococcus. The only question of importance is, how may this antigen be prepared to the best advantage? Schwartz and McNeil in their latest communication say that the "various strains of gonococci are grown on salt-free veal-agar, neutral in reaction to phenolphthalein; 24-hour old cultures are washed off the agar-slants with distilled water and the resulting suspension is heated for two hours in a water-bath at 56 C. It is then centrifuged and passed through a Berkefeld filter. No salt is added to this antigen until it is desired to use it, when it is made up to 0.9 per cent. strength by adding one part of 9 per cent. saline solution to nine parts of antigen. Following Schwartz and McNeil's instructions to the letter, we have prepared monovalent, trivalent and hexavalent antigens[2] and have employed them comparatively in a large series of cases with the result that the hexavalent preparation gave the highest percentage of positive results and in every way appeared to be the most reliable of the three antigens. Even with the hexavalent antigen,[3] prepared as described above, we have been forced, in comparative studies, to the conclusion that it has not been so useful or reliable as when prepared in the following manner: Forty-eight-hour old cultures of the same six strains of gonococci, grown on blood-agar, were washed off in sterile distilled water; shaken for one hour; and autolyzed for twenty-four hours in a thermostat at the temperature of 37 C. and heated in a water-bath at 60 C. for one-half hour. Before use, this antigen is diluted one to ten by the addition of 0.85 per cent. salt solution. In spite of our efforts[2] thus far, we have been unable to produce an antigen showing results quite as clean-cut, although they have been just as constant, as that marketed by

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[2] In the near future we shall report the results of our studies of various gonococcal antigens, variously extracted; also the results comparatively of non-specific antigens prepared from certain Gram-negative and Gram-positive diplococci, as the *Micrococcus catarrhalis*, the meningococcus, the pneumococcus, the *Streptococcus pyogenes*, etc.

TABLE 1—

	No. Test Tube	Antigen (Dilution 1:10) c.c.	NaCl Solution (0.85%) c.c.	Patient's Serum (Inactivated) c.c.	Known Positive Serum (Inactivated) c.c.	Known Negative Serum (Inactivated) c.c.	Complement (Dilution 1:10) c.c.		Hemolytic Amboceptor (Antisheep) (Titre = 1:2,000) (Dilution 1:1,000) c.c.	Red Blood Corpuscles (Sheep's 5% Washed Suspension) c.c.
Tests for complement standardization.........	1	0.2 ?	1.3	...	...	...	0.2	Incubation at 37 C. for one hour.	1.0	1.0
	2	0.2 ?	1.2	...	...	...	0.3		1.0	1.0
	3	0.2 ?	1.1	...	...	...	0.4		1.0	1.0
	4	0.2 ?	1.0	...	...	...	0.5		1.0	1.0
Tests for antigen standardization and controls	5	0.05	1.5	...	0.1	...	0.4 ?		1.0	1.0
	6	0.1	1.4	...	0.1	...	0.4 ?		1.0	1.0
	7	0.2	1.3	...	0.1	...	0.4 ?		1.0	1.0
	8	0.3	1.2	...	0.1	...	0.4 ?		1.0	1.0
	9	0.2	1.3	...	...	0.1	0.4 ?		1.0	1.0
	10	0.4	1.1	...	...	0.1	0.4 ?		1.0	1.0
	11	0.6	0.9	...	...	0.1	0.4 ?		1.0	1.0
Tests and controls for the suspected serum	12	0.2	1.3	0.1	...	...	0.4		1.0	1.0
	13	0.2	0.9	0.1	...	...	0.8		1.0	1.0
	14	0.2	1.3	0.1	...	...	0.4		1.0	1.0
	15	...	1.5	0.1	...	...	0.4		1.0	1.0

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[3] We are indebted to Dr. A. P. Hitchens of H. K. Mulford Co. for the six strains of gonococci employed in this work. It should be noted in this connection that it is assumed that the cultures are true gonococci, since their staining and morphological characteristics are identical with that micro-organism, although they grow readily on blood-serum or even on plain agar-agar. The dispute has arisen as to whether a Gram-negative diplococcus, growing in this wise, should or should not be designated as the *Micrococcus catarrhalis*.

Parke, Davis & Co. The probable explanation is that their antigen is made up from twelve strains of the gonococcus, while ours contains but six.[3]

ANALYSIS OF CASES TESTED

The result of our work has been little more than a corroboration of the reports that have emanated from Schwartz and McNeil[4] and those who have confirmed their results. We believe, however, that, by utilizing the technic herein described, we have added to the accuracy of the test as applied by them and have thereby improved the findings to the credit of the test and its value in clinical diagnosis. To the increased positive results we attribute the accurate standardization of antigen on each occasion and the employment of a standardized single complement unit. For the sake of convenience, our results with respect to the serums tested, numbering in all 204, have been tabulated (Table 2).

TEST REACTIONS

	Results (Immediately or Morning After Refrigeration)	Objects of the Reactions.
Incubation at 37 C., for one and one-half hours.	Incomplete hemolysis.....	To determine quantity of complement to be used in test proper.
	Incomplete hemolysis.....	To determine quantity of complement to be used in test proper.
	Complete hemolysis.......	To determine quantity of complement to be used in test proper.
	Complete hemolysis.......	To determine quantity of complement to be used in test proper.
	Incomplete hemolysis.....	To determine quantity of antigen to be used in test proper.
	Partial hemolysis.........	To determine quantity of antigen to be used in test proper.
	No hemolysis............	To determine quantity of antigen to be used in test proper.
	No hemolysis............	To determine quantity of antigen to be used in test proper.
	Complete hemolysis.......	To prove that the antigenic dose is not in itself anticomplementary.
	Complete hemolysis.......	To prove that twice the antigenic dose is not in itself anticomplementary.
	Incomplete hemolysis.....	To prove that thrice the antigenic dose is not in itself completely anticomplementary.
	No hemolysis............ (Positive reaction hemolysis = 1 unit)	To determine quantitatively the degree of complement fixation.
	No hemolysis............ (Positive reaction hemolysis = 2 units)	To determine quantitatively the degree of complement fixation.
	Complete hemolysis....... (Complete negative reaction)	Shows that there was no immune body present in the patient's serum with the aid of the antigen to fix the complement.
	Complete hemolysis.......	Proves that the immune body itself will not fix complement.

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[4] Schwartz and McNeil: "The Complement-Fixation Test in the Diagnosis of Gonococcic Infections," Am. Jour. Med. Sc., May, 1911; "The Complement-Fixation Test in the Differential Diagnosis of Acute and Chronic Gonococcic Arthritis," ibid., September, 1912; "Further Experiences with the Complement-Fixation Test in the Diagnosis of Gonococcus Infections of the Genito-Urinary Tract in the Male and Female," ibid., December, 1912.

TABLE 2.—RESULTS WITH RESPECT TO SERUMS TESTED

KNOWN NON-GONORRHEAL AFFECTIONS

No.	Remarks	Result of Gonococcus Complement-Fixation Reaction. Antigens: Monovalent (Unfiltered)	Trivalent (Filtered)	Parke, Davis & Co. (Schwartz Technic.)	Hexavalent Unfiltered	Parke, Davis & Co.
1	Typhoid fever				Negative	Negative
2	Typhoid fever				Negative	Negative
3	Typhoid fever				Negative	Negative
4	Tuberculous otitis media and pulmonitis				Negative	Negative
5	Tuberculous otitis media and pulmonitis					Negative
6	Pulmonary tuberculosis				Negative	Negative
7	Diabetes mellitus				Negative	Negative
8	Diabetes mellitus				Negative	Negative
9	Diabetes mellitus				Negative	Negative
10	Acute streptococcic endocarditis				Negative	Negative
11	Chorea; secondary endocarditis				Negative	Negative
12	Malaria				Negative	Negative
13	Syphilis					Negative
14	Congenital syphilis					Negative
15	Syphilis					Negative
16	Luetic rhinitis					Negative
17	Syphilis					Negative
18	Syphilis				Negative	Negative
19	Normal, no symptoms of gonorrhea					Negative
20	Normal, no symptoms of gonorrhea					Negative
21	Normal, no symptoms of gonorrhea	Negative	Negative	Negative		Negative
22	Tuberculous osteitis and pulmonitis					Negative
23	Chronic hypertrophic arthritis				Negative	Negative
24	Subacute arthritis (sacro-iliac and elbow)				Negative	Negative
25	Arthritis (both ankles); six weeks					Negative
26	Tuberculous arthritis (knee)				Negative	Negative
27	Chronic synovitis (midtarsal)					Negative
28	Optic atrophy					Negative
29	Neurasthenia					Negative
30	Neurasthenia					Negative
31	Chancroid					Negative
32	Vesical calculus; cystitis					Negative
33	Hemiplegia					Negative
34	Myelitis; incontinence of urine	Negative				Negative
35	Case of rape; no signs of infection	Negative		Negative		Negative

36	Epididymitis, possibly tuberculous, but undoubtedly gonorrheal	....	....	....	Medium +	Medium +
37	Urine cloudy and full of shreds	Medium +	....	....	....	Strongly +
	PATIENTS CLINICALLY CURED					
38	Several attacks of gonorrhea; no signs at present	....	....	....	....	Weakly +
39	Convalescent after treatment for 2½ years for chronic urethritis and prostatitis	....	....	....	....	Negative
40	Syphilis; had three doses of neosalvarsan; convalescent from chronic urethritis	....	....	....	....	Negative
41	Convalescent from chronic prostatitis	....	....	....	....	Negative
42	Convalescent from chronic urethritis, three attacks; first 3 years ago	....	....	....	....	Negative
43	Convalescent from first attack of gonorrhea 8 weeks previously	....	....	....	....	Negative
44	Convalescent from attacks of gonorrhea 13 and 2 years previously	....	....	....	Negative	Negative
45	Gonorrhea several years ago; no symptoms now	....	....	....	Negative	Negative
46	Clinically convalescent from gonorrhea acquired 2 years ago	....	....	....	....	Negative
47	Convalescent from urethritis and prostatitis; received 8 c.c. of antigonococcic serum 15 months ago for gonorrheal pleurisy	....	....	....	Negative	Negative
48	Polyarthritis; has gonorrheal history	....	....	....	....	Negative
49	Gonorrhea three times; asserts a cure; complains of impotence	Medium +	....	....	....	Strongly +
50	Gonorrhea 3 years ago; epididymitis 9 months ago; prostatorrhea; wants to marry	....	....	....	....	Negative
51	Gonorrhea three or four times; now clinically cured	....	....	....	....	Negative
52	Gonorrheal history; apparently cured	Negative	Negative	Negative	....	Negative
53	Gonorrhea 5 months ago; cured	....	....	....	....	Negative
54	Contracted gonorrhea 1½ years ago; convalescent from chronic prostatitis	....	....	....	....	Negative
	CASES ACCIDENTALLY DISCOVERED. CLINICALLY CURED					
55	Confessed to gonorrhea 2½ years ago; under antisyphilitic treatment	Weakly +	....	....	....	Weakly +
56	Luetic rhinopharyngitis; no inquiry as to gonorrhea	....	....	....	....	Weakly +
	ACUTE ANTERIOR URETHRITIS					
57	Gonorrhea of 12 hours duration (first attack)	....	....	....	....	Negative
58	Gonorrhea of 10 days' duration (first attack)	....	....	....	....	Negative
59	Acute gonorrhea (first attack)	....	....	....	....	Negative
60	Gonorrhea of 11 days' duration (first attack)	....	....	....	....	Negative
61	Gonorrhea of 7 days' duration (first attack)	....	....	....	....	Negative
62	Gonorrhea of 4 weeks' duration (first attack)	....	....	....	Negative	Negative

TABLE 2.—RESULTS WITH RESPECT TO SERUMS TESTED.—(Continued)

No.	Remarks	Result of Gonococcus Complement-Fixation Reaction. Antigens: Monovalent (Unfiltered)	Trivalent (Filtered)	Parke, Davis & Co. (Schwartz Technic.)	Hexavalent Unfiltered	Parke, Davis & Co.
	ACUTE AND SUBACUTE ANTERO-POSTERIOR URETHRITIS					
63	Gonorrhea of 6 weeks' duration (first attack)	....	....	....	....	Medium +
64	Gonorrhea of 5 weeks' duration (first attack)	....	....	....	....	Negative
65	Gonorrhea of 4 weeks' duration (first attack 10 years ago)	....	....	....	....	Negative
66	Gonorrhea of 2 weeks' duration (first attack)	....	....	....	....	Negative
67	Gonorrhea of 10 days' duration (first attack 1 year ago	....	....	....	....	Negative
68	Gonorrhea of 7 weeks' duration (first attack)	....	....	....	....	Negative
69	Gonorrhea of 4 weeks' duration (first attack)	....	....	....	Negative	Negative
70	Gonorrhea of 6 weeks' duration (first attack)	....	....	....	Negative	Negative
71	Gonorrhea of 7 days' duration (three previous attacks)	....	....	....	Negative	Negative
72	Gonorrhea of 10 days' duration (six previous attacks)	....	....	....	Negative	Negative
73	Gonorrhea of 5 week's duration (first attack 2 years ago)	....	....	....	....	Negative
	CHRONIC URETHRITIS PLUS ACUTE EXACERBATION					
74	Gonorrhea 1 year previously; received 8 c.c. of antigonococcic serum; duration of present attack is 4 weeks	....	....	....	....	Weakly +
75	Gonorrhea 2 years previously; duration of present attack is 4 weeks	....	....	....	....	Medium +
76	Gonorrhea 1 year previously; duration of present attack is 3 weeks	....	....	....	....	Strongly +
77	Gonorrhea 1 year ago; acute exacerbation at present	....	....	....	....	Weakly +
78	Gonorrhea 8 times previously; duration of present attack is 17 days	Strongly +	Weakly +	Strongly +	....	Strongly +
79	Gonorrhea 5 years ago; duration of present attack 10 days	....	....	....	Weakly +	Weakly +

80	Gonorrhea 4 years ago; present attack of 8 months' duration	....	....	....	....	Medium +
81	Gonorrhea several times; present attack of 2 months' duration	....	....	....	....	Negative
82	First attack; duration of 6 months	....	....	....	....	Negative
83	Contracted gonorrhea 3 years ago	....	....	....	....	Weakly +
84	First attack; duration 3½ months	....	....	....	....	Negative
85	First attack; duration 6 months	....	....	....	....	Negative
86	First attack; duration 2½ months	....	....	....	....	Strongly +
87	Gonorrhea twice previously; present attack 3 months duration	....	....	....	....	Weakly +
88	First attack; duration 8 months	....	....	....	....	Negative
89	Gonorrhea several times; urine contains shreds	....	....	....	....	Negative
90	First attack; duration 5 months	....	....	....	....	Negative
91	Chronic gonorrhea; duration unknown	....	....	....	....	Negative
92	Gonorrhea 7 times in 12 years; duration of present attack unknown	....	....	....	....	Strongly +
93	Gonorrhea 4 years ago; duration of present attack unknown	....	....	....	....	Medium +
94	Gonorrhea 2 times previously; duration of present attack 2 years	Medium +	....	Medium +	....	Medium +
95	Gonorrhea 1½ years ago; present attack 5 months' duration	....	....	....	....	Negative
96	Gonorrhea 16 years ago; present attack of 9 months' duration	....	....	....	....	Negative
97	First attack; duration 1 year	....	....	....	....	Negative
98	First attack; duration 4 months	....	....	....	....	Negative
99	Urethritis for 12 years	....	....	....	....	Negative
100	Chronic urethritis; duration unknown	....	....	....	....	Strongly +
101	Gonorrhea one year ago; pain in heel	....	....	....	....	Negative
102	Chronic recurrent urethritis	Negative	Negative	Negative	....	Negative
103	Gonorrhea 2 years ago; duration of present attack unknown	....	....	....	....	Negative
104	Gonorrhea 2 years ago; slight morning discharge	....	....	....	....	Negative
105	Gonorrhea 3 times previously; present attack 3 months duration	....	....	....	....	Weakly +
106	Gonorrhea 5 years ago; present attack 4½ months' duration	....	....	....	....	Strongly +
107	Gonorrhea previously; duration of present attack 6 months	....	....	....	Weakly +	Weakly +
108	Gonorrhea 3 years ago; bilateral buboes	....	....	....	....	Negative
109	First attack; duration 15 months; had four inoculations of Gonorrhea Bacterin 1 year ago	....	....	....	Negative	Negative
110	Chronic urethritis; duration unknown	....	....	....	Negative	Negative
111	Gonorrhea for years; several recurrences	....	....	....	Negative	Negative
112	First attack; duration 2 months	....	....	....	Negative	Negative

TABLE 2.—Results with Respect to Serums Tested.—(Continued)

No.	Remarks	Result of Gonococcus Complement-Fixation Reaction. Antigens: Monovalent (Unfiltered)	Trivalent (Filtered)	Parke, Davis & Co. (Schwartz Technic.)	Hexavalent Unfiltered	Parke, Davis & Co.
113	Recurrent; duration at least 1 year	....	....	....	....	Weakly +
114	Second attack gonorrhea 1 year ago; prostatitis and seminal vesiculitis treated for 1 year; practically cured at present	....	....	....	....	Negative
115	Duration 6 months	....	....	....	....	Negative
116	Gonorrhea 4 years ago; recurrent prostatitis, seminal vesiculitis and stricture ever since	....	....	....	....	Weakly +
117	Gonorrhea 1 year ago and 5 months ago	....	....	....	Medium +	Medium +
118	First attack of gonorrhea 1 year ago; never cured	Negative	....	....	....	Strongly +
119	Gonorrhea 8 years ago; not treated; now has shreds in urine	....	....	....	....	Negative
120	Gonorrhea 6 years ago; discharge at present	....	....	....	....	Strongly +
121	First attack of gonorrhea 1 year ago; chronic posterior urethritis and prostatitis	....	....	....	....	Medium +
122	First attack of gonorrhea 3 months ago	....	....	....	....	Negative
123	Duration uncertain	....	....	....	....	Weakly +
124	Has had gonorrhea nine times; last attack 6 months ago	Negative	Negative	Negative	....	Negative
125	First attack of gonorrhea 9 years ago; last attack 2 years ago	....	....	....	....	Negative
126	Duration unknown	....	....	....	....	Negative
127	Gonorrhea 3 years ago and continuously ever since	....	....	....	....	Medium +
128	Gonorrhea past 4 years; second attack	....	....	....	....	Negative
129	First attack of gonorrhea 5 years ago; never cured	....	....	....	....	Doubtful
130	Duration unknown	Medium +	....	....	....	Strongly +
131	Gonorrhea twice before; present attack of 4 years' duration	Medium +	....	Medium +	....	Strongly +
132	Gonorrhea 9 months ago; discharged as cured from another hospital; still has shreds in urine	....	....	....	....	Weakly +
133	Duration one year	....	....	....	....	Negative
134	Gonorrhea five times	....	....	....	....	Medium +
135	Duration unknown	....	....	....	....	Negative
136	Gonorrhea four times; last time 8 months previously	....	....	....	....	Weakly +
137	Gonorrhea 4 years ago; last attack 2 months ago	....	....	....	....	Negative

138	Ten or twelve attacks of gonorrhea; last attack 6 months ago	....	....	....	....	Negative
139	Gonorrhea 2 years previously; shreds in urine	....	....	....	....	Weakly +
140	Gonorrhea one year ago	Weakly +	Weakly +	....	....	Strongly +
141	First attack; duration 1 year	....	....	....	....	Negative
142	Chronic hypertrophic changes in knee joint; prostatitis	Negative	....	....	....	Negative
143	Gonorrhea for four years	....	....	....	....	Strongly +
144	Gonorrhea contracted 5 years ago; now has mild prostatitis and stricture	....	....	....	....	Negative
145	Gonorrhea 4 years ago; now has prostatitis and seminal vesiculitis	....	....	....	Negative	Negative
146	First attack of gonorrhea 6 years ago; present recurrence one year ago (mild)	....	....	....	....	Negative
147	Duration unknown; has taken gonorrheal phylacogen without benefit	....	....	....	....	Medium +
148	Several attacks of gonorrhea over period of 10 years; had forty four inoculations of gonococcic bacterin in 6 months 2 years ago	....	....	....	....	Weakly +
149	Same case 1 week later; under treatment	....	....	....	....	Negative
150	Gonorrhea 2 years ago	....	....	....	....	Negative
151	Gonorrhea first time 5 years ago; twice since; duration of prostatis 1½ years; three recurrences; last one 9 months ago	....	....	....	....	Negative
152	Recurrence of above case 2 months later	....	....	....	....	Negative
153	Gonorrhea 26 months ago; very slight; involvement of prostate; urine clear	....	....	....	Negative	Negative
154	Duration unknown; case 155, 10 days after treatment	Negative	....	Negative	....	Negative
155	Gonorrhea 5 years ago	....	....	....	....	Weakly +
156	First attack; duration 6 months	....	....	....	....	Weakly +
157	Above case three weeks later	....	....	....	....	Weakly +
158	Gonorrhea 3 years previously	....	....	....	....	Weakly +
159	Gonorrhea 15 years ago; last 2½ years ago; premature ejaculation	Weakly +	Weakly +	....	....	Strongly +
160	Gonorrhea 7 and 2 years; present attack of 4 mos.' duration; had 5 injections of phylacogen	....	....	....	....	Medium +
	STRICTURE					
161	Gonorrhea 3 years and 4 months ago	....	....	....	....	Medium +
162	Gonorrhea 14 and 12 years ago	Negative	Negative	Negative	....	Negative
163	Gonorrhea for 1½ years	....	....	....	....	Negative
164	Two attacks of gonorrhea; last one 18 months ago	Negative	....	Strongly +	....	Weakly +
165	Gonorrhea for 4 years with recurrences	....	....	....	Strongly +	Medium +
166	Duration unknown	....	....	....	....	Strongly +

TABLE 2.—Results with Respect to Serums Tested.—(Continued)

No	Remarks	Result of Gonococcus Complement-Fixation Reaction. Antigens				
		Monovalent (Unfiltered)	Trivalent (Filtered)	Parke, Davis & Co. (Schwartz Technic.)	Hexavalent Unfiltered	Parke, Davis & Co.
	EPIDIDYMITIS					
167	Duration three weeks	....	....	....	....	Negative
168	Same as 167, two weeks later	....	....	....	....	Weakly +
169	Epididymitis 2½ months ago; still unresolved; prostatitis	....	....	....	....	Medium +
170	First attack of gonorrhea; duration unknown	....	....	....	....	Medium +
171	Gonorrhea and epididymitis 2 years ago; second attack at present	Weakly +	Weakly +	....	....	Strongly +
172	Gonorrheal history; slight swelling of epididymis	Negative	Negative	....	....	Medium +
173	Previous attack of gonorrhea; present attack of six weeks' duation	....	....	....	....	Medium +
174	Gonorrhea three or four times; last time six weeks ago	....	....	....	....	Weakly +
175	First attack of gonorrhea; duration six months	Negative	Weakly +	Strongly +	....	Strongly +
176	Gonorrhea twice previously; present attack of six weeks' duration	Negative	Strongly +	....	....	Strongly +
177	Acute attack of nine days' duration	....	....	....	....	Weakly +
178	Acute attack of seven days' duration; denies gonorrhea	....	....	....	....	Medium +
179	Gonorrhea three times previously; epididymitis 15 years ago, plus present attack	....	....	....	....	Strongly +
180	Duration two months	Strongly +	Medium +	....	....	Strongly +
181	Duration unknown	....	....	....	....	Medium +
182	Bilateral epididymitis, probably tuberculous; has pulmonary tuberculosis; gonorrhea 10, 5 and 2 years ago	....	....	....	....	Negative

183	Chronic hypertrophic arthritis; duration 1 year; abdominal section 3 years ago; no G. U. symptoms at present	....	....	....	....	Medium +
184	Arthritis knee for 10 years; urethritis for 6 months, since when knee has been worse	....	....	....	....	Weakly +
185	Multiple subacute arthritis; no history of gonorrhea	Weakly +	....	Weakly +	....	Weakly +
186	Arthritis both ankles; gonorrhea for 3 years; synovitis 3 weeks after gonorrhea	....	....	....	....	Weakly +
187	Duration 10 weeks	....	....	....	Weakly +	Weakly +
188	Pain in left shoulder; no inquiry as to gonorrheal history	....	....	....	....	Weakly +
	GYNECOLOGICAL CASES					
189	Pain in right ovarian region; leukorrhea; dysuria; frequency	....	....	....	....	Negative
190	Eclampsia	....	....	....	Negative	Negative
191	Puerperal sepsis	....	....	....	Negative	Negative
192	Pelvic abscess; puerperal sepsis	....	....	....	Weakly +	Weakly +
193	Abscess of uterine cornua; vaginal smear shows Gram-diplococci	....	....	....	Negative	Negative
194	Abscess in cornua of uterus; delivered of dead fetus	....	....	....	Negative	Negative
195	Leukorrhea; dysuria; frequency	....	....	....	Negative	Negative
196	Vaginal smear shows Gram-diplococci	....	....	....	Negative	Negative
197	Vaginal smear shows Gram-diplococci	....	....	....	Negative	Negative
198	Tenderness in hypogastrium; vaginal smear shows Gram-diplococci	....	....	....	Negative	Negative
199	Tenderness in hypogastrium; vaginal smear shows Gram-diplococci	....	....	....	Negative	Negative
200	Salpingitis	....	....	....	....	Negative
201	Pyosalpingitis	....	....	....	Negative	Negative
202	Gonorrheal urethritis; salpingo-oöphorectomies	....	....	....	....	Medium +
203	Bartholinitis and cyst	Negative	....	....	....	Negative
204	Gonorrheal endometritis	....	....	....	....	Strongly +

Reviewing our experience with the gonococcus complement-fixation test in general, it may be stated that a negative reaction is not decisive against the presence of a gonorrheal infection, and this is particularly true during the first six weeks of a primary acute urethritis either anterior or posterior in the absence of any complication, previous to which time we have never obtained a positive reaction; on the other hand, the supervention, even during the acute stage of the disease, of complications such as epididymitis, arthritis, prostatitis, etc., is prone to result in the production of a positive reaction. On the contrary in our experience, a positive reaction has been pathognomonic of a focus of gonococcal infection and has assisted many times in elucidating obscure or doubtful lesions. In fact, it appears that the gonococcus-fixation test enjoys greater specificity than does the Wassermann reaction, since thus far we have found no alien infection or condition capable of producing a positive reaction. This much certainly cannot be claimed for the Wassermann reaction. Moreover, there is no drug, as there is in syphilis, which is capable of causing the reaction to be negative during the existence of the disease. The probable explanation for the greater specificity of the gonococcus complement-fixation test rests in the fact that with gonococcic infections we employ a specific antigen—the gonococcus—while in the case of syphilis a non-specific or lipotropic antigen is employed.

The analysis of our cases further illustrates another interesting feature, namely, the persistence in some cases for a short time of a positive reaction, after an apparent clinical cure. This has occurred so often that we no longer discharge a patient cured or give him a clean bill of health so long as he gives a positive reaction, provided he has not been the recipient of immunotherapy. Usually a persistent positive reaction will become negative in two or three weeks following clinical cure with or without a continuation of treatment. The only explanation is that it requires an indefinite time for the antibodies, formed during the course of infection, to disappear from the blood. Torrey,[5] in animal experimentation, has found that the antibodies in immunized rabbits begin to disappear after ten days, and that the elimination is practically complete by the fiftieth day in all cases, disappearing much earlier in many instances. Thus a patient, evidencing a positive reaction two months after presumed clinical cure, should be regarded as still harboring a latent gonorrheal focus. Such experience, adopted either as routine procedure in the management of treatment, or discovered accidentally when gonorrheal infection or its symptoms were denied, or demonstrated by submitting suspected or positive syphilitic serum to the gonococcus-fixation test, has been encountered in a large number of cases.

Because of the generally acknowledged difficulties, at times, of differentiating the pelvic lesions in women, notably certain of the inflammatory from the cystic and neoplastic conditions, and also the differential diagnosis among gonorrheal, tuberculous and pyogenic infections themselves, the gonorrheal-fixation test seems destined to play a rôle. As in the male, in whom a positive reaction seems never to occur, at least so long as the infection is confined to the anterior urethra, so in the female we have been unable to obtain a positive reaction unless the disease has ascended to the level of the uterus.

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[5] Torrey: Jour. Med. Research, 1910, No. 1.

An interesting, if not important, feature connected with this work is the comparative importance and value of the serological and bacteriological examination of cases of suspected gonorrheal infection. It is, to-day, a fact that the judiciary courts of our land require that the presence of the gonococcus be demonstrated, culturally, in order to establish its indisputable and legal identity. Based on this qualification, there are many cases of gonococcic infection impossible to determine, and we do not hesitate to state that, in our judgment, many such cultures are in reality the *Micrococcus catarrhalis* and not the gonococcus. This applies particularly to such isolation of the diplococcus of Neisser from chronic inflammatory processes. Moreover, it must be generally recognized that the demonstration of a Gram-negative diplococcus in smear is often insufficient and faulty evidence on which to base a diagnosis of gonococci. Therefore, it is most fortunate that in the chronic stage of the disease with complications, the complement-fixation test seems to be signally meritorious, while in the acute, subacute and frequently in the chronic forms of the diseases when the gonococcus may be demonstrated bacteriologically, the serological test promises little or nothing.

CONCLUSIONS

Detailed and careful analysis of the gonococcus complement-fixation test, performed with the serums of the cases tabulated in our series, would seem to justify the following assertions:

1. A positive reaction is invariably reliable and always denotes the presence of a focus of gonococcic infection.

2. A negative reaction frequently fails to determine the presence of disease especially in the acute and subacute stage when the disease is limited to the urethra, and never when it is confined to the anterior urethra or vagina alone.

3. In no alien non-gonorrheal infections of systemic disease has a positive reaction been obtained; the test, therefore, appears to be absolutely specific.

4. A positive reaction has been found to be present in 21.05 per cent. of patients clinically cured. Such patients, therefore, should not be discharged from treatment or observation until a negative reaction has been obtained.

5. Not infrequently, either when suspicious lesions are presented or accidentally, positive reactions will be discovered in patients denying gonorrhea.

6. In only 9.09 per cent. of cases of acute and subacute anteroposterior urethritis has the complement-fixation test resulted positively. The earliest appearance of a positive reaction in a primary attack of posterior urethritis, without complication, occured in the sixth week.

7. In a number of cases of chronic recurrent urethritis with acute exacerbations, the test was invariably positive; many of these patients undoubtedly had prostatitis.

8. The reaction resulted positively in one-third of all cases of chronic posterior urethritis; undoubtedly many of these cases had a mild or low-grade prostatitis.

9. In 52.08 per cent. of cases of chronic prostatitis a positive reaction was obtainable.

10. Two-thirds of all stricture cases demonstrated a positive test.

11. In epididymitis a positive complement-fixation test was observed in 87.5 per cent. of cases. If, from our series, one case probably tuberculous, may be eliminated, and a time duration of five weeks can be imposed, the positive result in this form of disease has been 100 per cent.

12. In arthritis, undoubtedly gonorrheal in character, positive reactions were obtained in 100 per cent. of cases.

13. In the diagnosis and differential diagnosis of pelvic disease in women, the gonococcus-fixation test is destined, unquestionably, to play an important rôle. We have been unable to obtain any positive results in uncomplicated urethritis, vulvovaginitis and Bartholinitis, and it would appear that the infection must ascend at least to the level of the uterus in order to produce a positive blood response.

14. Inoculations of gonococcus bacterin, antigonococcic serum, etc., may in themselves by the production of immune bodies be causes of positive reactions. How long these immunizing effects may endure is unknown, but we have observed patients, treated by immunotherapy, who one year later demonstrated negative complement-fixation reactions.

15. Although the bacteriological demonstration of the gonococcus culturally is the only absolute method for its identification in chronic inflammatory processes, the method as a routine procedure is impractical and susceptible of many failures and fallacious results, so that the complement-fixation test is not only less laborious, but is productive of a higher percentage of positive findings.

16. Finally, we hope and trust that the complement-fixation tests in gonococcic infections, as the Wassermann reaction in syphilis, are demonstrating their reliability and value to the extent that they will be recognized as indispensable, so soon as the courts shall rule that each applicant for marriage licensure must produce a health certificate properly attested.

A COMPARISON OF THE EXCRETORY POWER OF THE SKIN WITH THAT OF THE KIDNEY THROUGH A STUDY OF HUMAN SWEAT *

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The fact that the skin and the kidneys can act, to a certain extent, vicariously, seems to be generally accepted, as is manifest by the use of sweat-baths in the treatment of uremia. The skin excretes, qualitatively, practically the same substances which occur in the urine, namely, urea, ammonia, uric acid, amino-acids,[1] creatinin,[2] chlorids, phosphates, sulphates and certain enzymes.[3] The quantity of these substances, however, excreted by the skin is, normally, far less than that eliminated through the kidneys.

In health the ratio of the quantities of the various urinary constituents to one another is fairly constant, independent of the actual amounts of the substances eliminated by the kidney. Moreover, this ratio for urine differs from that existing between the same substances in the blood-stream. Hence the kidney exercises a selective concentrating action for certain substances. The question then suggests itself as to whether or not any such relation exists between the normal constituents of sweat, and, further, if any definite relation obtains between the quantities of the substances eliminated through the skin and kidneys. Such a similar relationship of the urinary and sweat factors would tend to show a similar selective power between the skin and kidneys.

Favre and later Kast[4] studied the relationship between the chlorids, phosphates and sulphates in the urine and sweat. The results show no outspoken relationship between the mineral constituents of the two fluids. These investigators found the ratios shown in Table 1 between these substances in sweat and urine.

Aliprando Moriggia[5] has noted the similarity of substances excreted both in sweat and urine, but showed the presence of an acid sweat in experimental alkalinuria in man, while in herbivora an experimental

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* Submitted for publication, Aug. 7, 1913.

[1] Embden and Tachau: Biochem. Ztschr., 1910, xxviii, 230.

[2] Capranica, S.: Maly's Jahresb., 1882, xii, 190.

[3] Gaube, M. J.: Compt. rend. Soc. de Biol., 1891, xliii (Addenda), 115.

[4] Kast: Ztschr. f. physiol. Chem., 1887, xi, 501.

[5] Morrigia, A.: Moleschott's Untersuchungen zur Naturlehre, 1876, xi, 129.

acid urine was always accompanied by alkaline sweat. This would tend to show some distinct selective power of the skin and kidneys, but is not conclusive, as the reaction of sweat may depend on the admixture of secretion from the sebaceous glands.[6]

TABLE 1.—Chlorids, Phosphates and Sulphates in Urine and Sweat According to Studies of Favre and Kast

	Chlorids	Phosphates	Sulphates	
Favre	1	trace	0.043	sweat.
	1	0.0959	0.380	urine.
Kast	1	0.0015	0.009	sweat.
	1	0.1320	0.397	urine.

W. Mironowitsch[7] found more mercury excreted in the sweat than in the urine after subcutaneous injection of mercury salt during treatment for syphilis. Argutinsky,[8] in an examination of two samples of sweat obtained by means of a vapor bath, determined the urea nitrogen, ammonia nitrogen and total nitrogen. The urea nitrogen amounted to 68.4 per cent. and 75.0 per cent. of the total nitrogen, and the ammonia nitrogen to 3.1 per cent. and 5.8 per cent. of the total. W. Camerer, Jr.,[6] in two cases found the urea nitrogen to be 34.6 per cent. and 34.0 per cent., and the ammonia nitrogen 8.0 per cent. and 6.6 per cent. of the total.[1]

J. H. Hoelscher[9] undertook a rather comprehensive study of the chemical composition of human sweat. His method of obtaining sweat consisted in wrapping the subject in sterile gauze, exposing to a dry heat of not more than 120 F. for a period of one or two hours, and then subjecting the gauze to pressure to obtain the fluid. The specific gravity, reaction toward litmus, total solids, organic and inorganic, urea and total nitrogen are reported, but the fact that the methods adopted for the analyses are nowhere mentioned considerably lessens the value of this work. Calculations which we have made from his data on the relationship between the urea nitrogen and total nitrogen of the sweat in twenty-four cases of normal passive sweat show the urea nitrogen to vary between 36 per cent. and 100 per cent. of the total. The majority of the values show a more constant relationship between urea and total nitrogen, but the extreme variation before noted is untenable. Moreover, his figures

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6. Trumpy, D. and Luchsinger, B.: Arch. f. d. ges. Physiol. (Pflüger's), 1878, xviii, 494. Arloing, S.: Lyon méd., 1896, No. 50. Camerer, Jr., W.: Ztschr. f. Biol., 1901, p. 1271.

7. Mironowitsch, W.: Medic. Koje Obostenze, No. 12 (through St. Petersburg med. Wchnschr. Beilage, 1895, 39).

8. Argutinsky: Arch. f. d. ges. Physiol. (Pflüger's), 1890, xlvi, 594.

9. Hoelscher, J. H.: Jour. Am. Med. Assn., 1899, xxxii, 1352; N. Y. Med. Jour., 1904, lxxix, 296.

are higher in general than those which were obtained later by L. Riggs[10] and also by us.

Recently Riggs has made a short study of six normal cases and three nephritics[11] on the partition of the nitrogen of the sweat. The total nitrogen, urea and ammonia were determined, as well as certain inorganic constituents. We cite here the relationship existing between the ammonia nitrogen and urea nitrogen, as percentages of the total nitrogen, as presented in his report.

TABLE 2.—PERCENTAGES OF THE TOTAL NITROGEN[12] AS CALCULATED BY RIGGS

Urea Nitrogen	Ammonia Nitrogen
47.3	8.1
63.6	9.1
52.0	14.0
54.8	5.5
57.7	7.0
48.0	7.2

Tichborne claims to have detected uric acid in sweat obtained in a Turkish bath, using the murexid test.[13] Hoelscher states that uric acid is not a constituent of normal sweat. Riggs tested 400 c.c. of sweat according to Salkowski's method, but found no indication of uric acid or purin bodies. Uric acid appears to have been recognized as a constituent of pathological sweats, however; that is, in gout and rheumatism.[14]

In the course of this investigation, eight cases of normal passive sweat have been examined for uric acid and its presence demonstrated in each instance.

Our experiments have embraced a determination of the nitrogenous constituents only, with the addition of an estimation of the diastatic activity. The age and weight of the subject, the quantity of sweat eliminated in twenty-five minutes and the increase in body temperature during the procedure were noted in order to ascertain if any relation exists between these factors. The total nitrogen, urea nitrogen and ammonia nitrogen, with the addition of uric acid and diastase, in some specimens, were estimated. The normal values and relationship between

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[10] Riggs, Louis: Jour. Med. Research, 1911, xix, 285.

[11] Although twenty-six analyses are reported on nephritic sweat, these specimens of sweat were in reality obtained from three patients who were subjected to repeated sweat baths.

[12] This author has calculated the combined urea and ammonia nitrogen as percentages of the total, and has laid no emphasis on the percentages of the relative values here given.

[13] Tichborne, C. R. C.: Brit. Med. Jour., 1887, ii, 1097.

[14] Hammersten: Mandel Text-Book of Physiological Chemistry, Ed. 6, p. 800.

TABLE 3.—CHEMICAL DETERMINATIONS IN SWEAT BEGAN WITHIN AN HOUR AFTER OBTAINING THE SAMPLE

Case No.	Age	Weight	Appearance time	Duration minutes	Temperature before	Temperature after	Amount obtained c.c.	Specific Gravity	Reaction	Total N per cent.	Urea N Per Cent.	Ammonia N Per Cent.	Uric Acid Per Cent.	Diastase $D^{38°}_{24}$
1	23	220	30	25	....	.....	330	1.009	Acid	0.194	0.132	0.0159	....	...
2	28	180	25	45	....	.....	102	1.009	Acid	0.136	0.077	0.0098	....	...
3	22	165	20	25	98.4	99.8	50	1.007	Acid	0.067	0.033	0.0084	....	...
4	20	185	20	25	98.0	99.6	93	1.011	Neutral	0.107	0.056	0.0056	....	...
5	23	220	15	25	98.4	99.8	323	1.008	Acid	0.085	0.034	0.0073	0.00012	...
6	25	125	25	25	98.4	102.6	93	1.015	Acid	0.118	.....	0.0087	....	...
7	20	175	20	25	98.4	100.6	190	1.009	Neutral	0.070	0.035	0.0053	....	...
8	26	170	20	25	98.4	100.6	175	1.007	Acid	0.068	0.035	0.0070	0.00018	...
9	21	185	20	25	98.6	99.8	64	1.007	Acid	0.105	0.059	0.0094	....	...
10	37	160	25	25	98.0	98.2	260	1.009	Neutral	0.069	0.039	0.0059	0.00014	...
11	22	178	30	25	98.4	101.0	120	1.009	Acid	0.175	0.102	0.0104	....	...
12	24	175	20	25	98.2	100.2	420	1.007	Acid	0.059	0.031	0.0056	0.00009	...
13	25	190	20	25	98.2	98.8	196	1.008	Acid	0.090	0.041	0.0053	0.00014	1.1
14	34	190	15	25	98.5	99.8	270	1.007	Acid	0.055	0.026	0.0047	0.00010	1.0
15	22	185	15	25	....	.....	245	1.011	Neutral	.....	.....	......	0.00005	2.1
16	23	165	20	25	....	.....	340	1.007	Neutral	.....	.....	......	0.00007	1.0
17	28	210	20	25	98.2	98.8	80	1.009	Neutral	.....	.....	......	....	1.1
18*	22	190	20	27	....	.....	180	1.008	Acid	0.127	0.078	0.0115	....	0.6

* During the procedure of sweating this case, 5 gm. of urea, dissolved in 100 c.c. of distilled water were injected by gravity intravenously, during a period of three minutes. The blood and urine of the subject were collected immediately before and shortly after the sweating. No appreciable increase of the amount of urea present was found in either fluid after the injection.

these substances in blood and in urine are well recognized. Consequently, a comparison of the relationships with those of the sweat should prove instructive.

EXPERIMENTAL METHODS

Method.—The subjects chosen were normal male adults, living on a mixed diet, not rich in proteins. The cardiorenal and gastro-intestinal tracts were within range of normal, and none of the subjects were of neurotic type. The experiments were performed at approximately the same hour, about four hours after a breakfast, consisting of eggs, bread and coffee, no abnormal exercise having been indulged in in the interim. After rubbing the skin with 95 per cent. alcohol, the subject was placed in a rubber bag 7 feet long by 4 feet in circumference, on a simple wicker couch, the upper end of which was raised 8 inches. The bag itself was then caught up where necessary by large clamps to conform closely to the body of the subject, thus minimizing the air-space around him, and reducing the possible error of evaporation to a minimum. Above this bag, and surrounding it entirely, was a rubber-lined air-chamber, 1 by 3 by 6 feet, into the side and top of which was projected the mouth of a pipe 6 inches in diameter, conducting hot air. The end of the hot-air tube was protected below by a fan-shaped cuff of cardboard to prevent the possibility of heat being unduly concentrated. No water was given the subject immediately before sweating. Temperatures were taken by mouth at the beginning and end of the experiment. From the time of appearance of perceptible sweat, to the conclusion of the procedure an arbitrary period of twenty-five minutes was chosen, and in most cases this was amply sufficient to secure an amount of fluid large enough for all chemical investigation.

In every case the sweat was filtered through ordinary filter-paper to remove any cast-off epidermal débris. As used for investigation, it was a slightly opalescent liquid. Examination of several specimens microscopically gave no evidence whatever of cellular content. The chemical determinations were undertaken within an hour after obtaining the sample.

Methods of Analysis.—Specific gravity was estimated by hydrometer. Each sample was tested as to its reaction toward litmus paper. The total nitrogen was determined in the usual way by the Kjeldahl-Gunning method, the urea by the method recently developed by one of us for blood,[15] and the ammonia by the aeration method.[16] The uric acid determinations were made by the colorimetric method recently described by Folin for the estimation of uric acid in the blood,[17] using 100 c.c. to 200 c.c. for each determination. The diastase determinations were made by the method of Wohlgemuth.[18] The principle of this method depends on estimating the smallest quantity of the fluid to be tested which can completely change 5 c.c. of 1 per cent. starch solution (Kohlbaum's *Stärke löslich*) in twenty-four hours at 38 C., to products not capable of giving any blue color with iodin. In the case of sweat, owing to the small amount of diastase present, we have used a 0.5 per cent. or 0.25 per cent. starch solution, and referred the value to a 1 per cent. solution. That this procedure gives reliable results was determined by duplicate experiments, using larger quantities of sweat and a 1 per cent. starch solution. The diastatic activity of the urine and blood-serum was estimated by the same method. The values for diastase are expressed in terms of the number of cubic centimeters of a 1 per cent. starch solution which 1 c.c. of the fluid in question can change in twenty-four hours at 38 C. to products not capable of producing any blue color with iodin. This is designated as $D^{38}/_{24}$.

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[15] Marshall, Jr., E. K.: Jour. of Biol. Chem., 1913, xv, 487.

[16] Folin: Ztschr. f. Physiol. Chem., 1902-03, xxxvii, 2261.

[17] Folin: Jour. Biol. Chem., 1913, xiii, 469.

[18] Wohlgemuth: Biochem. Ztschr., 1908, ix, 1.

RESULTS

Table 3 gives a general summary of the results obtained. A uniformity of the time necessary to produce perceptible sweat is evident. The figures cited would suggest that body-weight does not always effect a proportionate change in the amount of sweat or total nitrogen eliminated. Case 6 shows an amount of 93 c.c. and 0.1097 gm. of nitrogen eliminated for a body-weight of 125 pounds, while Case 3 shows an amount of only 50 c.c. and 0.0385 gm. of nitrogen eliminated for a body-weight of 165 pounds. No definite relationship apparently exists between the amount of nitrogen eliminated and an increase in body temperature during the procedure. Case 5 shows a very high output of nitrogen (0.2758 gm.) and no marked rise of temperature (99.8 F.), while Case 6 shows a comparatively lower output of nitrogen (0.1097 gm.) and a temperature of 102.6 F. Though this test was not carried out on the same subject, we feel that the observation is of value, as it is corroborated so many times throughout the table.

Although the absolute amount of any one constituent, normally eliminated, may vary between rather wide limits in different specimens. there exists a fairly constant ratio between the amount of urea, ammonia and total nitrogen excreted.

From the numerous investigations by Boland, Schultze, Camerer, Voges, Morner-Sjoqvist, Gumlich, Bodtker, Folin[19] and others on the relationship of different nitrogenous constituents to each other in normal *urine,* it is shown that the urea nitrogen amounts to from 84 to 91 per cent. and the ammonia nitrogen from 2 to 5 per cent. of the total nitrogen. The relation between the total nitrogen, urea nitrogen and ammonia nitrogen of *sweat* calculated from figures in Table 3 is shown in Table 4.

The urea nitrogen varies from 45.6 to 68 per cent. of the total, with a mean of 53.7 per cent.; while the ammonia nitrogen amounts to from 5.2 per cent. to 12.4 per cent. of the total, with a mean of 8.1 per cent. Hence it is apparent that the relationships between the different forms of nitrogen in sweat and urine are entirely different. In regard to the relationships existing between the various forms of non-protein nitrogen in *blood,* satisfactory data are far too scanty to draw any general conclusions. The urea nitrogen in normal blood amounts roughly to about 50 per cent. of the total non-protein nitrogen, while no apparent relationship between the amount of uric acid and urea or total non-protein nitrogen seems to exist.[20] The figures for uric acid show a very different relationship in sweat from that in blood and in urine, although the data are insufficient to tell whether or not any constant relationship exists between the uric acid and the total nitrogen of sweat.

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[19] Hammersten-Mandel Text-Book of Physiologic Chemistry, Ed. 6, p. 646 for a collection of the literature.

[20] Folin: Jour. Biol. Chem., 1913, xiv, 33.

The concentration of urea in blood is normally about 0.02 or 0.03 per cent. The kidney has the power of concentrating this about one hundred times, as the normal concentration in the urine is about 2 per cent. The sweat-glands can also concentrate urea, though to a much less degree, the concentration in sweat being about .05 to 0.3 per cent. Ammonia exists in extremely minute amounts normally in the blood, and in much greater concentration both in sweat and in urine; so both skin and kidney can concentrate ammonia. Uric acid exists normally in the blood in quantities ranging between 0.0007 and 0.0037 gm. per 100 c.c.;[21] in urine[22] between 0.015 and 0.080 gm. per 100 c.c., while in sweat we have found only from 0.00005 to 0.00018 gm. per 100 c.c. From this it is evident that the kidney does normally concentrate uric acid, while in the passage of fluid through the skin its concentration is much reduced. The concentration in sweat is only about one-twentieth that in the blood.

TABLE 4.—Percentage of Total Nitrogen Found in the Forms of Urea Nitrogen and Ammonia Nitrogen, Respectively

Case No.	Urea nitrogen	Ammonia nitrogen
1	68.0	8.2
2	56.6	7.2
3	49.7	12.4
4	52.6	5.2
5	46.6	8.5
6	....	7.4
7	49.9	7.5
8	51.5	10.2
9	56.0	8.9
10	55.9	8.4
11	58.3	5.9
12	52.2	9.5
13	45.6	5.8
14	47.3	8.5
18	61.4	9.0

Diastase, in general, may be said to occur in the urine in greater concentration than in the blood,[23] while the figures for sweat show a diastatic activity much lower than that of either blood or urine. Owing to the wide variation of diastatic activity of the blood, it was thought interesting to confirm this point by making diastase determinations on the blood, urine and sweat of the same subjects. The results show that, although the kidney normally concentrates the enzyme, the latter is much less concentrated in the sweat than in the blood.

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[21] Folin and Denis: Jour. Biol. Chem., 1913, xiv, 29.

[22] Folin and Denis: Jour. Biol. Chem., 1912, xiii, 363.

[23] Wohlgemuth: Biochem. Ztschr., 109, xxi, 381, 432.

The urine was collected immediately before and after sweating, and the blood withdrawn from the arm immediately after emergence from the bag. The values show the amount in cubic centimeters of 1 per cent. starch solution, which 1 c.c. of the fluid can change to products not capable of giving blue color with iodin in twenty-four hours at 38 degrees.

TABLE 5.—Diastatic Determination ($D^{38}/_{24}$) in Urine, Blood and Sweat.

	Urine		Blood	Sweat
Case No.	Before	After		
13	1.000	167	167	1.1
14	100	100	25	1.0
17	.....	166	25	1.1

COMPARISON OF THE EXCRETION OF DYES THROUGH THE SKIN AND KIDNEY

As far as concerns the excretion of non-toxic dye-stuffs through the skin, the following data show that the skin does not normally excrete the faintest trace of the substances used, which substances pass readily into the urine. Phenolsulphonephthalein was administered intramuscularly in 6 mg. doses in four normal individuals; the injection was made immediately before entering the bath, and the drug began to appear in the urine before the appearance of perceptible sweat and continued to be excreted after the sweating process was completed. In each of these cases the output of phthalein was normal in the urine, but not the slightest trace could be detected in the sweat even after concentration.[24] Experiments with methylene-blue were conducted in two ways. In one case, 8 grains were given in 4-grain doses, one hour apart, the last dose being given within thirty minutes of the time of appearance of perceptible sweat. Although the urine was deeply colored, both before and after collecting the sweat, no trace of methylene-blue could be found in the latter. In two other instances in which the subject had been given 12 grains of the drug per day for three days preceding the experiment, no color was obtained through the skin, though the urine both before and after the procedure was heavily pigmented.

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[24] In a series of forty cases of universal skin lesions of all types, including dermatitis exfoliativa, psoriasis universalis, eczema, ichthyosis, etc., studied by one of us (Plaggemeyer), phenolsulphonephthalein was excreted by kidneys in normal amounts. This drug evidently has a decided selective action for the kidneys and is not, in any way, affected by concomitant skin lesions. Article to be published later.

Indigo carmin was administered by injecting 4 c.c. of a 4 per cent. solution into the gluteus maximus, thirty minutes before sweating. The urine showed a deep blue color, indicating a high output of the drug, while the sweat, which was definitely acid, did not show the slightest trace. Rosanilin given under similar conditions in another case also failed to be excreted through the skin.

Phloridzin was injected in 5 mg. doses and readily produced a glycosuria, but in the two cases examined no trace of glucose could be detected in the sweat with Nylander's test.

Hexamethylenamin was tried in two cases. In one, the patient was given 35 grains in a moderate amount of water within two hours of sweating, and in the other the patient was on a daily régime of 45 grains. Both cases showed a definite excretion through the skin, which may explain the pruritus occasionally present in patients on a urotropin régime.

SUMMARY

The facts shown by this study of sweat from eighteen normal cases may be summarized as follows:

1. Uric acid and diastase are apparently constant constituents of normal sweat.

2. Body-weight does not necessarily effect proportionate change in the amount of sweat eliminated nor in the total nitrogen content.

3. No definite relationship exists between the amount of nitrogen eliminated and an increase in body temperature during the procedure.

4. The relationships between the different forms of nitrogen in sweat and urine are entirely different. The concentration of urea in sweat is from three to ten times as high as that in the blood, but only one-tenth (1/10) the concentration of urea in the urine.

5. The sweat-glands have the power of concentrating ammonia, and the ratio of ammonia nitrogen to the total nitrogen is considerably higher than that in the urine.

6. Uric acid occurs in sweat in much smaller amounts than in either blood or urine, the concentration being about one-twentieth (1/20) that in blood and about one five-hundredth (1/500) that in urine.

7. Diastatic activity, though slightly variable in sweat, shows a mean value, lower than that in either blood or urine.

8. The commoner dye-stuffs used for colorimetric estimation of kidney function are not eliminated through the skin.

9. Phloridzin injections are followed by a negative sugar reaction in sweat, although the reaction is positive in urine, from the same case.

CONCLUSIONS

It has been demonstrated that no apparent relationship exists between the chlorids, sulphates and phosphates excreted in urine and in sweat, and it has been repeatedly shown that the kidney concentrates urea, ammonia, uric acid and diastase. Our study has demonstrated that the glands of the skin concentrate urea and ammonia, but that the diastatic activity is less than that in either blood or urine, and that uric acid is present in less concentration than in the blood. The relative concentrating power of the skin and kidney for urea and ammonia are very different, though in both cases the percentage values are higher than those for blood. These facts, in conjunction with the fact that the kidneys show a decided selective action for many dyestuffs, while on the other hand, mercury seems to be more readily excreted through the skin, lead us to conclude that, under normal conditions, the skin and kidneys show a distinct selective action. The bearing of this on sweat-baths as a therapeutic measure in cases of uremia and nephritis is evident. The various substances which are producing toxemia in a given case may be among those which the kidney can concentrate, while in sweat they are found in less concentrated form than in the blood-stream. In the former case, sweating would not be indicated. Hence, certain reservations should be made on the efficacy of such procedures as a routine method of treatment and much further work remains to be done on the relation existing between skin and kidneys in pathological conditions, accompanied by cumulative phenomena in the blood-stream; with especial regard to obstruction in the urinary tract.

We are greatly indebted to Dr. H. H. Young for the clinical material on which this study is based.

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STATUS LYMPHATICUS IN ADULTS, ITS CLINICAL DIAGNOSIS AND IMPORTANCE *

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At the present time our knowledge of the condition recognized as status lymphaticus, or as it is more commonly called by German writers — status thymicolymphaticus, is not based on etiology, but on physical characteristics.

It is not essential to the pursuit of clinical studies that we should have a theory of the disturbed physiology, which determines the abnormal physical individual, nor yet await the complete understanding of the separate or mutual functions of the various secreting tissues, before we admit the relation of the clinical findings to health and disease. What is important for the internist, and for the eugenist, is the recognition of a type of individual whose physical peculiarities seem to bear an important relation to his mortality, in certain infectious diseases, and to his susceptibility to some of the deteriorating influences which modern society tolerates or suffers from. This recognition of a type of person, who may not appear less healthy or less capable than the rest of society, is at present based wholly on physical examination, one may almost say, on inspection alone.

Inspection of the human body provides us with physical signs of health or disease on which we rely. The value of physical signs, in relation to health and disease, depends on the constancy of association of the observed facts during life with a definite series of findings after death.

If the physical examination reveal constantly certain variations from the usual, or the accepted normal, and if the post-mortem examination reveal a constant series of gross and microscopical abnormalities in a tissue or groups of tissues, then where these two sets of observations are noted in a high per cent. of cases among those dying of certain of the infectious diseases, we may presume that there is some causal relation between the physical findings and the mortality of such individuals.

From the time when Paltauf (1889-90) pointed out the pathological symptom complex of status thymicolymphaticus, pathologists have more and more generally verified his observations, and in some instances have added to the data he gave in defining the condition found post mortem.

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When Neusser (1911) gave an equally clear description of the clinical picture of status thymicolymphaticus, an impetus was given to observations by the internists, to test their skill in establishing a reliable clinical diagnosis, with the possibility of its bearing on the prognosis or treatment of various diseases.

Having watched the cases of meningitis, typhoid fever, and septic infections in the general medical wards of Bellevue Hospital die apparently in a high percentage of cases when they showed the physical marks of status lymphaticus, and having noted at the autopsy table the constancy of pathological findings which confirmed the clinical description of such cases, I wished to test the reliability of the various criteria given for the recognition of a characteristic or classical case of status lymphaticus.

The material on which this study was based was at my disposal while attending the alcoholic wards at Bellevue Hospital in New York. These wards receive patients suffering from the toxic effects of alcohol and of other narcotic drugs, cases of attempted suicide and sick prisoners. Among the admissions are often to be found border-line cases, which, on further study, prove to be psychopathic cases rather than toxic individuals of normal mentality. One thousand cases were studied, five hundred consecutive male admissions in July and August, 1912, and an equal number in January and February, 1913.

The record of each patient consisted of the following points:

Age; country of birth; cephalic index, based on the occipitofrontal and biparietal diameters; the color and physical qualities of the hair of the head; the amount of hair on chin, the upper lip, on the chest in front, in the axillae, and the amount and distribution of pubic hair; the amount of faucial, lingual and pharyngeal lymphatic tissue, observed by inspection and digital palpation; the presence of palpable cervical, axillary and inguinal lymph-nodes; the shape and proportions of the neck, thorax, abdomen, thighs and upper arms; the details of the external genitals; the general nutrition; the presence of congenital anomalies; the clinical diagnosis.

Of the 1,000 cases examined, 780 were without any stigmata or physical characteristics which would mark them as abnormal.

Two hundred and twenty showed most if not all, of the physical attributes sufficient to identify them as cases of status lymphaticus.

Analysis of the records of these two groups shows certain facts.

As to age it was found that 18.63 per cent. of the status cases were under 30 years, while but 9.66 per cent. of the normal cases were under 30 years. Above the age of 30 the distribution of the status and of the normal cases showed such slight discrepancies as to lead to no conclusions. The patients' ages ranged from 19 to 84 years.

As to nationality or race the variations in the two classes were negligible. Eighteen nationalities were represented.

As to cephalic index, if we use the term dolichocephalic to represent an index of 80 or less and brachycephalic for an index of over 80, we find that the cases of status are almost equally divided, while the normal cases show a preponderance of 7 per cent. of dolichocephalics.

Status Lymphaticus, Per Cent.	Normal Cases, Per Cent.
Dolichocephalic, 49.14	53.63
Brachycephalic, 50.86	46.37

In noting the color, texture (i. e., fine or coarse), luster, curliness or straightness of the hair of the head, no differences of any importance were noted.

The beard was noted as being scanty in 9.87 per cent. of normal cases, but scanty or wholly lacking in 57.22 per cent. of the status cases.

Similarly it was found that the mustache was scanty in but 7.94 per cent. of the normal cases, but scanty or lacking in 55.90 per cent. of the status cases.

Sternal or anterior thoracic hair was found to be scanty in 41.15 per cent. of the normal cases, and scanty or wholly lacking in 89.54 per cent. of the status cases.

The axillary hair was scanty in 13.45 per cent. of the normal cases, but scanty or absent in 65.45 per cent. of the status cases.

The pubic hair was found to be of the feminine type (i. e., arranged transversely and not rising toward the umbilicus, but ceasing abruptly above the pubic region) in 13.20 per cent. of the normals, and in 95.90 per cent. of the status cases.

The faucial, lingual and pharyngeal tonsillar tissue was found increased in amount in the normal cases in 6.66 per cent., 26.02 per cent. and 4.48 per cent., respectively, and in the status cases in 7.27 per cent., 23.18 per cent. and 0.90 per cent., respectively; not notable differences except in the case of the pharyngeal tonsils. Even though the pharyngeal tonsil seems to be enlarged five times as often among status cases as in normal men, the percentage of incidence is too low to use for diagnostic purposes.

The case of the superficial lymph-nodes is somewhat similar, for although the cervical, axillary and inguinal nodes are found palpable in somewhat higher proportion of cases in the status individuals than among normals, the occurrence of such palpable glands in adults is so common as to allow of no diagnostic application of this point.

In normal cases the cervical, axillary and inguinal glands were palpable in 15.25 per cent., 33.33 per cent. and 53.71 per cent. respectively, and among status cases in 25.90 per cent., 41.81 per cent. and 55.90 per cent., respectively.

The neck was noted as long and slender in 32 per cent. of normals and in 36.81 per cent. of status cases—an unimportant difference.

The thorax was found long and narrow in 27.94 per cent. of the normal cases and in 44.09 per cent. of the status cases.

The contour of the abdomen as to its roundness or flatness showed no difference worth noting between the two classes.

The thighs were noted as rounded in 30.52 per cent. of the normal cases and arched in 13.97 per cent. of the normal cases, while in 75.46 per cent. of the status cases they were rounded and in 50 per cent. were arched. These terms, rounded and arched, are used to express the impression made by the difference between the masculine and feminine types of thigh, the rounded as contrasted with the flat thigh being characteristic of feminine physique, and an outward and forward bowing or arching being a feminine attribute as distinguished from the straighter masculine thigh.

In the case of the upper arm it was found that 25.76 per cent. of normal cases were described as having rounded arms, while among the status cases there were 75.90 per cent. with this feminine characteristic.

Among the normal cases the penis was noted as small in 22.56 per cent., while this was the case among the status cases in 51.83 per cent.

The glans penis was noted as small in normal cases in 26.03 per cent. and in status cases in 54.54 per cent.

The shape of the glans was described as pointed or acorn-shaped in normal cases in 32.05 per cent. and in status cases in 61.31 per cent.

There were no undescended testicles among the normal cases, but there were six cases or 2.7 per cent. found with undescended testicles among the status cases, four with both undescended, two with one undescended.

The size of the testicles was noted as small in 24.74 per cent. of normal cases, and among the status cases in 45.90 per cent.

As to general nutrition there were no differences of any moment.

Congenital anomalies were found in 0.25 per cent. of the 780 normal cases and in 3.63 per cent. of the 220 status cases.

Complicating medical affections, in addition to drug addiction, were found in 3.58 per cent. of the so-called normal cases and in 10.40 per cent. of the status cases; 94.4 per cent. of all cases were admitted for alcoholic intoxication.

To summarize the data obtained from these examinations, it may be said that 22 per cent. of the particular class of men representing chiefly the alcohol and narcotic drug habitués, show sufficiently striking variations from the usual masculine physical habit to be classed as cases of status lymphaticus; that, of the points usually noted in arriving at a diagnosis, those found to be constant enough to be entitled to consideration are, scantiness or absence of hair on lip, chin, and in sternal and axillary regions, together with the feminine type of distribution of pubic hair with or without scantiness of pubic hair; a tendency to narrowness and length in the thorax; a noticeable roundness and arching of the thighs and roundness of the upper arms; small size of penis; smallness and pointed shape of glans penis and smallness of the testicles.

In addition, there is a physical character noted in a very large proportion of the cases, and present almost invariably when the points above summarized are also present, namely, a particularly velvety, or fine and delicate texture of the skin, which is seen and felt to be almost wholly free from the usual short hairs, to be found commonly, for instance, on the thigh in men. For lack of such terms as would accurately designate this quality of the skin, I have not made a record of its appearance in the cases above reported, but I wish to call attention to this as an important diagnostic point.

Of the points described by others as commonly noted in cases of status which I find of little or no value in arriving at a diagnosis are, the physical characters of the hair of the head, which is supposed to be commonly coarse and straight in status cases; the faucial, lingual and pharyngeal lymph tissue, which is supposed to be commonly increased; the superficial lymph-nodes which are supposed to be felt in a high proportion of status cases; the slender columnar neck and the rounded feminine abdomen which are reported as being usual in status.

In addition, there is a point, described by European observers, which I have so regularly failed to make on physical examination of status cases, and which has so little foundation in the experience of the pathologists at Bellevue Hospital, that I have not made it a part of my records, namely, the spleen. The spleen is supposed to be large in status. This I do not find to be the case.

I am permitted by the Director of the Pathological Laboratory to quote from the forthcoming hospital report the results of autopsy records of status since 1905.

Of the 3,600 autopsies, 288, or 8 per cent., were cases of status lymphaticus.

Of these 288 cases, 29.66 per cent. were recessive cases, as shown by microscopical as well as gross study of the lymphatic tissues of the body, and 70.33 per cent. were active cases. Twenty-six of the 288 cases (or 9.02 per cent.) were not associated with other demonstrable lesions as a cause of death.

Two hundred and sixty-two (or 91.08 per cent.) were associated with other lesions.

Of these 262 cases, 242 were associated with infectious diseases.

Epidemic, purulent, or tuberculous meningitis.

Typhoid fever.

Lobar pneumonia.

Acute and chronic pulmonary, and general miliary tuberculosis.

Acute and chronic cardiac infections.

Septic infections of a variety of origins.

It is to be particularly noted that of the autopsied cases of typhoid fever 23.07 per cent. were status. Of autopsied cases of acute infective endocarditis 19.51 per cent. were status, and of the autopsied cases of epidemic cerebrospinal meningitis 48.27 per cent., while of the autopsied cases of lobar pneumonia 2.96 per cent. were status; of tuberculous meningitis 3.80 per cent. were status; of acute and chronic pulmonary or general miliary tuberculosis 4.50 per cent. were status.

In arriving at a pathological diagnosis at post mortem the essential points to be observed in addition to those accessible to the clinician during life, are the gross and microscopic appearance of the blood-vessels, particularly the aorta, which is small, soft and elastic; the intestinal lymph adenoid tissues, the Peyer's patches and follicles, and the mesenteric lymph-nodes which are uniformly found enlarged; either a hyperplasia of the lymph follicles of the spleen in active cases, or fibroid tissue tufts which have replaced previous hyperplasia of the lymph follicles in the recessive cases; enlargement of the thymus gland out of proportion to the age of the subject in active cases.

It is true that percussion and possibly Roentgen ray examination will, in the hands of a few, elicit the presence of an enlarged thymus in children, but the likelihood of this decreases with every decade of the patient's age above the first. By deep digital palpation in the episternal notch the normal aorta can usually be appreciated at each systolic impulse, and this is rarely the case in status cases, owing to the small size of the aorta, but this is of little reliability in arriving at a diagnosis.

For the present it seems to me that a diagnosis of status lymphaticus is justified, when we find, in the case of a man, a decided scantiness of hair on chin and upper lip, scanty axillary and sternal hair, scanty or feminine distribution of pubic hair; the slender thorax; rounded contour of upper arms and thighs with an arching of the latter; hypoplastic external genitals, particularly if associated with cryptorchismus; and a delicate velvety skin. The diagnosis is further confirmed if we find hyperplasia of the lymph tissue of nose, throat and tongue and an increase in the palpable cervical and axillary lymph-nodes.

If we admit the justice of such a diagnosis, because of the confirmation of a sufficient number of cases verified post mortem, of what service will this prove in the practice of medicine?

The obvious and justifiable conclusion at present is that such individuals are more susceptible to the dangers of infectious diseases than are normal people. To avoid for such people by all precautions, especially by artificial immunization, as for typhoid, diphtheria and meningitis, every chance of infection, is our evident duty. They are poor risks in an epidemic, and the prognosis for them, when they are infected, is more serious than for normal men. As they have passed the particular dangers of their state during childhood, by especial care or good fortune, so, during maturity, they are among those who cannot be expected to survive, as well as normal men, extreme fatigues, shocks, loss of blood, abuse of narcotic drugs or surgical procedures. Those physicians whose hospital experience is mainly with people of the upper walks of life, will undoubtedly find that the incidence of status lymphaticus is far below the figures I have presented here for alcoholic patients. And in the general medical wards of Bellevue Hospital, which receives almost exclusively the pauper class, the incidence is less than a quarter of that found among alcoholics.

Among psychopathic cases, particularly those who suffer acute alienation in the first three decades, the incidence of status is, I believe, even higher than among the cases I have reported above.

It should by no means be understood from this that all cases of status lymphaticus are undesirables, socially, as they may be physically less capable in the struggle for existence than their fellows, for it is in the experience of all who observe these cases that there are among them leaders in scientific and artistic professions, and men of the highest standards of character.

For the identification of status lymphaticus among women we rely on the peculiar character of the skin of the body and extremities, the scantiness of the axillary hair pad, the scantiness of pubic and perineal hair, hypoplasia of the genital apparatus, and particularly slender thorax and extremities. Some women of decided status conformity have a marked growth of hair on the face and upper lip. As has been pointed out by Paltauf, Bartel and others, the status cases among women are in a high percentage of cases subject to the dangers of pregnancy and the puerperium. With this addition, what has been said of male status cases applies equally to women.

While we await the embryological, or physiological, explanation for this particular physical habit (lymphatismus, hypoplastic constitution, constitutional inferiority, status thymicolymphaticus, or status lymphaticus), there is much which the clinician is equipped and particularly fitted to discover as to the relation between status lymphaticus and the incidence and course of various pathological states.

In closing, let me gratefully acknowledge my debt to Dr. Charles Norris, Director of the Pathological Laboratory at Bellevue Hospital, who was the first in the United States to recognize the clinical picture of status lymphaticus in adults, and place its diagnosis on a sound basis for clinician and pathologist.

Without his experience and records of the past seven years I could not have prepared this paper.

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STUDIES ON THE CIRCULATION IN MAN

XI. THE BLOOD-FLOW IN THE HANDS AND FEET IN CERTAIN DISEASED CONDITIONS OF THE VESSELS OR OF THEIR VENOUS MECHANISM *

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I. ARTERIOSCLEROSIS

It need scarcely be pointed out that several of the patients in the previous paper suffered from arteriosclerosis, in addition to valvular lesions of the heart or myocardial changes. In this section a few cases are brought together in which arteriosclerosis was pronounced and other lesions if present did not dominate the clinical picture. As a general result of the observations, it may be stated that in marked arteriosclerosis the flow in the hands is always smaller and the vasomotor reflexes weaker than in normal persons. Vasodilatation is easier to obtain by the application of warmth to the contralateral hand than vasoconstriction by the application of cold.

One of the purest cases of marked arteriosclerosis is that of Meyer G., a man aged 39, without detectable cardiac involvement. The flow was only 2.88 grams for the right hand and 3.46 grams for the left hand per 100 c.c. of hand per minute, with room temperature 22 C. An increase to 3.96 grams in the right was occasioned by immersion of the left hand in warm water, and the flow only fell to 3.52 grams when the left hand was subsequently put into cold water. It must not be forgotten, however, in connection with the small flow in this case that the man was a peddler accustomed to expose his hands in the open air in winter. Also he was a dispensary patient, and came from his work on a day in February.[1]

Meyer G., Hebrew peddler, aged 39, height 5 feet 6½ inches, was admitted at the dispensary Sept. 3, 1910, with marked arteriosclerosis. There was great thickening of all accessible arteries. The heart examination was negative in result. He complains of having had pain in the stomach during the past year. A test-meal showed free hydrochloric acid. No masses are palpable in the abdomen. He attributes his condition to strain in pushing heavy loads on his hand-cart. The hand flow was measured Feb. 3, 1911. He still complains of pain

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* From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

[1] See Paper IX of this Series, The Archives Int. Med., 1913, xii, 678.

in the epigastrium. On emptying capillaries on the back of the hand by pressure the color returns very slowly. Pulse, 72. Mouth temperature, 36.7 C. Systolic pressure in the right brachial, 110. Hands put into bath at 2:49 p. m.; into calorimeters at 2:59½.[2] Volume of right hand in calorimeter, 525 c.c.; of left hand, 525 c.c. He is right-handed. His hands are large. (Table 1.)

Another outside worker (John O'R.), a street laborer aged 60, with a diagnosis of arteriosclerosis and myocarditis, had a flow of 5.49 grams per 100 c.c. per minute in the right hand and 5.44 grams in the left hand with room temperature 23 C. The contralateral vasoconstriction to cold was slight, the flow in the right hand diminishing from 5.49 grams to 4.78 grams, but warmth gave a fair vasodilatation after the usual preliminary vasoconstriction. The protocol has already been published.[3]

TABLE 1.—Calorimetric Measurements in Case of Meyer G.

Time	Right	Left	Notes	Time	Right	Notes
2:58½	29.74	29.81		3:28	29.98	
3:01	29.69	29.75		3:29	30.00	
3:02	29.70	29.74	Room temp. 22.2 C.	3:30	30.02	
3:03	29.70	29.74		3:31	30.07	At 3:31 left hand put in water at 7.2 C.
3:04	29.70	29.74				
3:05	29.70	29.75		3:32	30.09	
3:06	29.70	29.75		3:33	30.11	
3:07	29.69	29.76		3:34	30.13	
3:08	29.69	29.75		3:35	30.16	
3:09	29.69	29.75		3:36	30.18	
3:10	29.69	29.78	Room temp. 22.3 C.	3:37	30.20	Room temp. 21.9 C.
3:11	29.71	29.80		3:38	30.21	
3:12	29.72	29.81		3:39	30.22	
3:13	29.73	29.82		3:40	30.23	
3:14	29.75	29.85		3:41	30.25	
3:15	29.77	29.89		3:42	30.27	At 3:42 left hand dried and wrapped in warm cloth.
3:16	29.78	29.90				
3:17½	29.80	29.93		3:43	30.29	
3:19	29.82	29.97		3:44	30.31	
3:20	29.83	30.00		3:45	30.33	
3:21	29.86	30.01	Room temp. 21.7 C.	3:46	30.36	Room temp. 22 C.
3:22	29.88	30.03		3:47	30.39	
3:23	.....	30.08	At 3:23 left hand put in water at 43 C.	3:48	30.42	
				3:49	30.45	Room temp. 22.2 C.
3:24	29.90	.....		3:50	30.48	At 3:50 hand out of calor.
3:25	29.92	.....		3:51	.....	Temp. of L. is now 29.75 C.
3:26	29.94	.....	Room temp. 21.6 C.	4:16	30.13	
3:27	29.96	.....		4:17	.....	Temp. of L. is now 29.48.

Charles S., a man aged 69, with sclerosed vessels, high blood-pressure and enlarged cardiac dulness, but no murmurs, had a flow in the right hand of only 5.25 grams per 100 c.c. per minute and in the left a flow of 5.01 grams, with the high room temperature of 28.3 C. The response of the vessels to reflex impulses from the contralateral hand was very poor, cold producing a small diminution in the flow, warmth no response whatever beyond the initial flow.

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[2] In all the observations unless otherwise stated the quantity of water in each hand calorimeter was 3,015 c.c.

[3] Cleveland Med. Jour., 1910, x, 385.

Charles S., a hammer man, aged 69, was admitted to Lakeside Hospital, June 26, 1911. He had gonorrhea forty-five years ago; never any chancre. He has been a heavy coffee and tea-drinker except in the last four or five years. He seldom drank whisky or beer, and smokes little. Six years ago following an attack of pneumonia he ate a heavy meal and immediately felt short of breath, dizzy and faint. He has had dizzy spells ever since. The attacks of dyspnea are worse at night and come on suddenly. Lately there has been swelling of the feet and ankles. There is Cheyne-Stokes respiration with periods of complete apnea lasting forty seconds. The anteroposterior diameter of the thorax is increased. There is difficulty in expelling air from the lungs. The cardiac dulness extends from 7 cm. to the right of the midsternal line in the fourth interspace to 14.5 cm. to the left of the midsternal line in the fifth interspace. The first sound at the apex is very tympanitic in quality with a slightly roughened element in it. Second sound normal, no murmurs or adventitious sounds. The blood-vessels are sclerotic. Pulse regular in rate and rhythm. The ascent is slow, no dicrotism. Blood-pressure: systolic, 180; diastolic, 120. Some edema of the skin of the genitalia and of the ankles is present. The skin is cool and dry. He has been on cardiac diet and treated with atropin and nitroglycerin. Hemoglobin, 95 per cent. Diagnosis, arteriosclerosis and myocarditis. He was discharged "improved," July 19, 1911.

TABLE 2.—CALORIMETRIC MEASUREMENTS IN CASE OF CHARLES S.

Time	Right	Left	Time	Right	Notes
2:45	.....	30.65	3:00	30.95	
2:46	30.61	.....	3:01	30.99	Room temp. 28.3 C.
2:47	.....	30.68	3:02	31.005	
2:48	30.67	.....	3:03	31.02	
2:49	.....	30.73	3:04	31.035	3:04 L. hand put in water at 43 C.
2:50	30.73	.....	3:05	31.055	Room temp. 28.3 C.
2:51	.....	30.77	3:06	31.09	
2:52	30.76	.....	3:07	31.11	
2:53	.....	30.825	3:08	31.125	
2:54	30.825	.....	3:09	31.135	
2:55	.....	30.87	3:10	31.155	
2:56	30.88	.....	3:11	31.20	At 3:11 hand out of calorimeter.
2:57	30.905	.....	3:12½	.....	Temp. of L. is now 30.76 C.
2:58	30.92	.....	3:29	31.08	Room temp. 28.15 C.
2:59	30.94	.....			

Cooling of calorimeters, R., 0.12 degree in eighteen minutes, L., 0.11 C. degree in seventeen and one-half minutes. Volume of right hand in calorimeter 437 c.c., of left hand 410 c.c.

The blood-flow in the hand was examined July 13, 1911. Mouth temperature, 36.3 C.; pulse (sitting), 80. Hands put into bath at 2:32 p. m.; into calorimeters at 2:44. At 2:55 p. m. left hand put into water at 8.5 C. Cooling of calorimeters, R., 0.12 degrees in eighteen minutes; L., 0.11 degree in seventeen and one-half minutes. Volume of right hand in calorimeters, 437 c.c.; of left hand, 410 c.c.

The last case to be referred to under this heading is that of Fred S., a man 58 years old, with pronounced arteriosclerosis of the vessels of the limbs, mitral insufficiency and pulmonary emphysema. The initial flow was 5.76 grams per 100 c.c. per minute for the right hand and 5.80 grams for the left hand, with an average room temperature of 23.8 C. Immersion of the left hand in warm water caused no change in the flow in the right for three minutes, an unusually sluggish reaction, but for the next ten minutes of immersion of the left hand in warm water the flow in the right rose to 7.69 grams per 100 c.c. per minute. Immersion of the left hand in cold water caused a reduction of the flow in the right to 3.65 grams per 100 c.c. per minute for the first three minutes, the flow then rising to 5.54 grams per 100 c.c. per minute for the next six minutes of immersion. When the left hand was again put into the warm water, there was only a small increase in the flow in the right (to 6.46 grams per 100 c.c. per minute for ten minutes' immersion).

TABLE 3.—Calorimetric Measurements in Case of Fred S.

Time	Right	Left	Room Temp. C.	Time	Right	Room Temp. C.	Notes
2:32½	31.09	31.07	....	3:00	31.78	....	
2:35	31.06	31.05	23.4	3:01	31.81	....	
2:36	31.07	31.05	....	3:02	31.855	24.0	
2:37	31.08	31.06	23.6	3:03	31.895	....	At 3:03 left hand put in water at 8 C. He feels it very cold and withdraws hand intermittently.
2:38	31.095	31.07	....	3:04	31.91	....	
2:39	31.11	31.08	....	3:05	31.92	23.9	
2:40	31.125	31.10	24.0	3:06	31.925	....	
2:42	31.17	31.15	....	3:07	31.95	....	
2:43	31.195	31.165	.....	3:08	31.975	24.0	
2:44	31.22	31.185	.....	3:09	31.995	....	
2:45	31.25	31.22	23.8	3:10	32.02	....	
2:46	31.29	31.26	.....	3:11	32.04	24.0	
2:47	31.32	31.29	.....	3:12	32.06	....	At 3:12 left hand put in water at 38.5 C.
2:48	31.36	31.34	23.9	3:13	32.085	....	
2:49	31.395	31.37	....	3:14	32.11	....	
2:50	31.425	31.40	.....	3:15	32.13	24.2	
2:51	31.45	.....	23.9	3:16	32.165	....	
2:52	31.48	.....	.....	3:17	32.195	....	
2:53	31.505	.....	.....	3:18	32.22	24.2	
2:54	31.54	.....	24.0	3:19	32.24	....	
2:55	31.59	.....	.....	3:20	32.27	....	
2:56	31.62	.....	.....	3:21	32.295	....	
2:57	31.66	.....	23.9	3:22	32.32	....	At 3:22 hand out of calor.
2:58	31.70	.....	.....	3:23	.....	....	3:23 Temp. of L. is 31.00 C.
2:59	31.74	.....	24.0	3:45	32.02	....	3:45 Temp. of L. is 30.79 C.

Fred S., a laborer, aged 58, was admitted to the City Hospital April 27, 1913, with marked arteriosclerosis, pulmonary emphysema and mitral insufficiency.

He complains of shortness of breath (asthma) which began in October last. He has not been able to work since. He says the condition seems stationary, neither improving nor growing worse. When he gets chilled an attack is brought on. The point of maximal cardiac impulse is 5 cm. outside the left nipple line. The greatest breadth of cardiac dulness extends at the sixth rib to the anterior axillary line; right border, right sternal margin. Roughened first sound at apex followed by systolic murmur, which is lost as the base is approached. Pulse fairly regular rhythm and rate, fair volume. Liver enlarged. Urine contains no albumin. A few hyaline and finely granular casts. Hot baths seemed to have a good effect on him.

The blood-flow in the hands was examined May 8, 1913. Hands in bath at 2:22½ p. m., in calorimeters at 2:33½. At 2:50 p. m. left hand put into water at 43 C. (Table 3.)

Cooling of calorimeters, R., 0.30 degree in twenty-three minutes, L., 0.61 degree in fifty-five minutes. Pulse (sitting) 116. Volume of right hand 497 c.c., of left hand 484 c.c. Rectal temperature 37.4 C. Water equivalent of calorimeters with contents, R., 3.492, L., 3.482. Blood-pressure left arm, systolic 126, 63 (sound gone). Another observation. Systolic 122, 101 (sudden diminution of sound), 63 (sound gone).

II. AORTIC ANEURYSM

If we leave out of account John M., a dispensary case who came in with cold hands on a winter day and could not wait for sufficient time to warm up and whose measured flow (3.96 grams per 100 c.c. per minute for the right hand) is therefore certainly too low,[4] a point of some consequence comes out in Table 19 in which the results are summarized; that is, that for the age of the patient and the temperature of the room the hand flow in these cases of thoracic aneurysm are either of the normal order of magnitude or at least not so conspicuously deficient as in those cases dealt with in Paper X, in which the stress of the pathological change falls on the myocardium rather than on the blood-vessels.

John M., an iron-molder, aged 32 years, weight 140 pounds, height 5 feet, 3½ inches, was admitted at the dispensary suffering from aortic aneurysm as shown by the Roentgen ray. He complains of pain over the sternum. Systolic blood-pressure, right arm 155, left arm 150. Blood-flow in the hands examined Feb. 13, 1911. Pulse (sitting) 72. Mouth temperature 37.0 C. Room temperature 22.2 C. His hands were cold when he came in. Right hand in bath at 2:56 p. m., in calorimeter at 3:07 and out of calorimeters at 3:36. At 3:25 left hand put into water at 8.5 C.

It is not, of course, suggested that in some of the cases of aneurysm deterioration and disordered function of the myocardium or crippling of the valves may not be of graver import than the aneurysm itself. But so far as the aneurysm, or rather the underlying condition which has occasioned the aneurysm has not led to deterioration of the heart, there is no reason in the mechanics of the circulation why the blood-flow through the hand should suffer. This is true even where the form of the pulse-wave may be greatly distorted by its passage through the aneurysmal sac. Of course, a sufficient degree of pressure of the sac on a subclavian artery or vein may diminish the flow in the corresponding hand. The great difference in the flow in the two hands in Paul K. may be accounted for by the pressure of the aneurysm on the left subclavian artery. The flow in his hands (for the last fifteen minutes in the calorimeters) was 7.64 grams for the right per 100 c.c. per minute and 5.9 grams for the left, with room temperature 22.6 C. (a ratio of 1.3:1). For the right hand this flow is not markedly subnormal for his age. The diagnosis was auricular fibrillation with mitral insufficiency (and stenosis), well compensated at the time of the blood-flow examination and aortic aneurysm. There is no evidence that the aneurysm, unless by its mechanical pressure, caused any change in the flow.

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[4] The fact that immersion of the left hand in cold water caused only a very slight diminution in the flow in the right while immersion of the left hand in warm water increased the flow decidedly (to 5.5 grams) indicates that the vasoconstriction produced by the exposure of the hand to the cold was initially considerable.

TABLE 4.—Calorimetric Measurements in Case of John M.

Time	Right	Time	Right	Time	Right
3:06	29.15	3:19	29.28	3:29	29.47
3:10*	29.13	3:20	29.30	3:30†	29.48
3:11	29.14	3:21	29.32	3:31	29.50
3:12	29.14	3:22	29.33	3:32	29.51
3:13	29.16	3:23	29.36	3:33	29.54
3:14	29.19	3:24	29.38	3:34‡	29.58
3:15	29.21	3:25	29.40	3:35	29.62
3:16	29.23	3:26	29.42	3:36	29.67
3:17	29.24	3:27	29.425	3:53	29.49
3:18	29.27	3:28	29.44	3:55	29.47

* Room 22.0 C. † At 3:30 left hand dried and wrapped up. ‡ Room 22.4 C. Volume of right hand 380 c.c.

Paul K., a baker, 57 years old, was admitted to the City Hospital Feb. 21, 1912. There is a history of lues and of frequent acute attacks of articular rheumatism. A history of skin rash was obtained. He had gonorrhea ten or twelve times. His present illness began three weeks before admission. He had an attack of rheumatism at the time and began to be short of breath. His eyes have been swollen for three days. There is bulging over the heart. The thorax is barrel-shaped, and many dry râles can be heard. A loud systolic murmur can be heard over the apex, the heart is very irregular. Not all the heart-beats are felt at the wrist. Blood-pressure is 110 to 120. The Roentgen ray shows a marked prominence of the aortic arch on the left side and heart enlarged. He was put on digitalis. The pulse-rate, which was 132 on the morning after admission, fell rapidly. During March and April it varied between 75 and 90, his clinical condition improved and he was allowed to leave his bed and walk about the ward.

The blood-flow in the hands was examined April 24, 1912. Hands in bath at 1:32 p. m., in calorimeters at 1:42¾, and out of calorimeters at 2:06. (Table 5.)

Cooling of calorimeters in ten minutes, R., 0.13 degree; L., 0.12 degree. Volume of right hand 454 c.c., of left hand 451 c.c. He works mainly with his left hand although he is right-handed. Rectal temperature 38 C. Water equivalent of calorimeters with contents, R., 3,458; L., 3,456. After the examination it was noticed that the heart-rate was much increased (to 140 counted with a stethoscope) and that it was more irregular than before.

In Joseph C., a dispensary patient aged 50, with marked arteriosclerosis, a high systolic pressure (160 mm.) and distinctly dilated aortic arch, the flow was 6.69 grams for the right hand and 6.66 grams for the left, with room temperature 21.5 C. Considering the amount of arteriosclerosis and that in arteriosclerosis, as already stated, the hand flow has a tendency to be diminished, there is no evidence in this case that the presence of the aneurysm as such has reduced the flow.

Joseph C., an iron molder, aged 50, height 5 feet, 9½ inches, was admitted to the dispensary Jan. 30, 1911. He has been ill for six or seven years, during which time he has done no work. Six years ago he lost consciousness and after that his left arm was paralyzed. The grip of the left hand is weak, too weak, he says, to grasp objects; but on testing this the difference between the hands is not great. He gets very dizzy at times. There is much arteriosclerosis. He suffers from pain in the head, also in the breast and in the left hand. The Roentgen ray shows a definite dilatation of the arch of the aorta. Wassermann reaction negative on Feb. 6, 1911.

TABLE 5.—CALORIMETRIC MEASUREMENTS IN CASE OF PAUL K.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
1:42	31.13	31.29	....	1:56	31.40	31.465	....
1:44	31.07	31.21	....	1:57	31.45	31.50	....
1:45	31.08	31.21	22.8	1:58	31.49	31.525	22.6
1:46	31.095	31.225	....	1:59	31.51	31.53	....
1:47	31.11	31.23	....	2:00	31.56	31.58	....
1:48	31.13	31.25	22.8	2:01	31.605	31.61	....
1:49	31.165	31.29	....	2:02	31.65	31.635	....
1:50	31.19	31.31	....	2:03	31.70	31.67	....
1:51	31.21	31.32	....	2:04	31.75	31.71	22.6
1:52	31.25	31.35	....	2:05	31.795	31.75	....
1:53	31.29	31.38	22.9	2:06	31.83	31.76	....
1:54	31.32	31.41	....	2:16	31.70	31.64	....
1:55	31.37	31.43	....	....	.....	.....	....

The hand flow was examined on Jan. 31, 1911. Hands in bath at 2:52 p. m., in calorimeters at 3:05, and out of calorimeters at 3:20; 3,056 c.c. of water in each calorimeter. Pulse (sitting) 88. Mouth temperature 37.2 C. (Table 6.)

Cooling of calorimeters, R., 0.19 degree, and L. 0.16 degree in fourteen minutes. Volume of right hand 505 c.c., of left 480 c.c. Blood-pressure, systolic in right brachial 160, in left brachial 164.

In William B., a man aged 53, suffering from thoracic aneurysm, the flow in the right hand was 8.38 grams per 100 c.c. per minute and in the left 7.33 grams with room temperature 20.8 C. (for fourteen minutes in calorimeters). The systolic pressure was very high (205 mm.). He was still taking nitroglycerin at the time of the blood-flow examination.

A second examination made at the dispensary nearly four weeks later showed a flow of 10.23 grams per 100 c.c. per minute for the right and 9.47 grams for the left hand, with room temperature 22.2 C. These flows are certainly not small for a man of his age and with sclerosed arteries. The inequality in the flow in the two hands is no greater than may be seen in normal persons, and it will be observed that the ratio between the flows in the two hands is the same at the two examinations (1:1.08).

TABLE 6.—Calorimetric Measurements in Case of Joseph C.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3:04	29.13	29.12	20.3	3:16	29.55	29.51	....
3:06	29.11	29.10	....	3:17	29.61	29.53	21.5
3:07	29.14	29.11	....	3:18	29.67	29.62	....
3:08	29.18	29.12	21.5	3:19	29.72	29.67	....
3:09	29.20	29.14	....	3:20	29.78	29.71	....
3:10	29.25	29.19	....	3:32	29.61	29.58	....
3:11	29.29	29.22	....	3:34	29.59	29.55	....
3:12	29.34	29.31	....	....	.....	.....	....
3:13	29.39	29.33	21.4	....	.....	.....	....
3:14	29.45	29.39	....	....	.....	.....	....
3:15	29.51	29.43	....	....	.....	.....	....

TABLE 7.—Calorimetric Measurements in Case of William B. First Examination

Time	Right	Left	Time	Right	Left
2:37	28.38	28.54	2:48	28.70	28.82
2:40	28.34	28.53	2:51	28.90	29.00
2:42	28.39	28.58	2:53	29.04	29.11
2:43	28.43	28.61	2:55	29.20	29.22
2:45	28.56	28.70	2:56	29.27	29.28
2:46	28.61	28.75	3:12	29.09	29.10

William B., a man aged 53, height 5 feet, 2 inches, weight 152 pounds, had an aneurysm of the thoracic aorta involving the innominate also to some extent. After being under observation at the dispensary for a considerable time he was admitted to Lakeside Hospital where he was under treatment for a month (digitalis and nitroglycerin). His hand flow was examined at the time of his discharge from the hospital. He felt much better than when he entered, on Dec. 22, 1910. He has no cough but there is a history of cyanosis, although there is no cyanosis now. He says his hands always feel rather cool, especially when his heart is bad.

Hands in bath at 2:26½ p. m., in calorimeters at 2:38½, and out of calorimeters at 2:56; 3,050 c.c. of water in each calorimeter. Room temperature 20.4 C.

Room temperature at end of observations 21.2 C. Volume of right hand in calorimeter 410 c.c., of left hand 390 c.c. Cooling of calorimeters in sixteen minutes 0.18 C. degree. Pulse (sitting) 84. Mouth temperature 37.1 C. Water equivalent of calorimeters with contents, R., 3.458; L., 3,442. (Table 7.)

The second examination was on Jan. 17, 1911. He says he feels about the same as at the first examination, only the shortness of breath on exertion is greater. Systolic blood-pressure 210. Hands put into bath at 3:09 p. m., in calorimeters at 3:21, and out of calorimeters at 3:37; 3,050 c.c. of water in each calorimeter. Room temperature 22.2 C.

TABLE 8.—Calorimetric Measurements in Case of William B. Second Examination

Time	Right	Left	Time	Right	Left
3:19	30.70	30.49	3:31	31.13	30.86
3:23	30.69	30.48	3:32	31.19	30.91
3:25	30.79	30.57	3:33	31.23	30.94
3:26	30.86	30.62	3:34	31.29	31.00
3:27	30.92	30.67	3:35	31.34	31.07
3:28	30.97	30.71	3:36	31.39	31.11
3:29	31.02	30.77	3:37	31.44	31.16
3:30	31.07	30.81	4:00	31.12	30.85

Cooling of calorimeters in twenty-three minutes, R., 0.32 C. degree; L., 0.31 C. degree. Volume of right hand in calorimeter 435 c.c., of left 410 c.c. Mouth temperature 36.9 C. Water equivalent of calorimeters with contents, R., 3,478; L., 3,458. Pulse (sitting) 88.

In Richard B, a man aged 38, with a large aortic aneurysm extending, as shown by the Roentgen-ray, to a considerable distance to the right of the sternum, there was a decided deficiency in the flow of the left hand as compared with the right (10.91 grams per 100 c.c. per minute for the right, 8.15 grams for the left, a ratio of 1.33:1). For the room temperature of 28 C., 10.9 grams is not a large flow, but neither is it decidedly small. The vasomotor reflexes from the right to the left hand were normal in direction, and not strikingly deficient in intensity, showing that the chief afferent path in the vasomotor reaction to warmth or cold (the nerves of warmth and cold sensation) have not appreciably suffered by stagnation of the circulation due to the pressure of the aneurysm on the right subclavian vein. Now, when pressure is maintained on the arm at a level somewhat below the systolic arterial pressure by means of the cuff of a sphygmomanometer the warmth sensation suffers early, so that it is impossible to appreciate the contact of a warm tube, while the sensation of pain is at this stage less affected. As has been pointed out in Paper X, a certain amount of venous distention, provided that the arterial pressure is correspondingly increased, may even be associated with an increased flow, because of the increased cross-section of the smaller vessels. So far as the arterial path to the right arm in Richard B. is concerned, the conditions would favor a greater flow in the right hand, for as shown at the necropsy the aneurysm provided a much wider entrance than normal for the blood going to the right subclavian and possibly a reservoir which helped to maintain the flow during diastole.

Richard B., a colored gardener, aged 38, height 5 feet, 7½ inches, was admitted to Lakeside Hospital May 22, 1911, with an aneurysm diagnosed as aortic. He complains of hoarseness during the past two weeks and vomiting during the past week, also cough. He admits lues. There is a tender pulsating mass in the suprasternal notch with fulness in the right supraclavicular region. Heart 3 cm. to left of nipple. A distant systolic murmur at the supraclavicular notch. The aortic second is slightly accentuated. There is distinct diastolic shock, unilateral (right) distention of veins, and clubbing of fingers. The Roentgen ray shows an enormous shadow upward and to the right. The patient continued in the hospital until his death, Aug. 22, 1911. There was no right radial pulse for the last week of life. Blood examination on May 23, 1911, showed hemoglobin 95 per cent., leukocytes 5,000. June 1 the Wassermann test was strongly positive. The necropsy showed a saccular, spherical aneurysm of the innominate artery 3 to 4 inches in diameter. The arch of the aorta was not involved except for the somewhat enlarged ring at the beginning of the innominate opening into the sac.

Hand flow examined May 23, 1911. Pulse (sitting) 100. Mouth temperature 37.1 C. Hands put into bath at 2:44 p. m., into calorimeters at 2:54½. At 3:08 p. m. right hand put into water at 8.1 C.

TABLE 9.—Calorimetric Measurements in Case of Richard B.

Time	Right	Left	Room Temp. C.	Time	Left	Room Temp. C.	Notes
2:54	30.43	30.38	....	3:13	31.225	....	
2:55	30.475	30.42	27.7	3:14	31.28	....	
2:56	30.53	30.43	....	3:15	31.325	28.0	
2:57	30.595	30.46	....	3:16	31.36	....	At 3:16 put right hand in water at 43 C.
2:58	30.695	30.525	....	3:17	31.38	....	
2:59	30.78	30.60	....	3:18	31.415	....	
3:00	30.86	30.63	....	3:19	31.46	....	
3:01	30.935	30.69	27.9	3:20	31.525	28.3	
3:02	31.02	30.74	....	3:21	31.58	....	
3:03	31.12	30.825	....	3:22	31.625	28.2	
3:04	31.20	.....	....	3:23	31.67	....	
3:05	31.295	30.93	....	3:24	31.725	....	
3:06	31.34	30.98	....	3:25	31.80	....	
3:07	31.395	31.02	....	3:26	31.85	28.2	Hand out of calorimeter.
3:08	31.46	31.035	....	3:41	31.75	28.0	Temp. of R. is now 31.27 C.
3:09	.....	31.07	28.0				
3:10	.....	31.10	....				
3:11	.....	31.125	....				
3:12	.....	31.155	....				

Cooling of calorimeters, R., 0.19 degree in thirty-three minutes; L., 0.10 C. degree in fifteen minutes. Volume of right hand 495 c.c., of left 437 c.c. There is an obvious difference in the size of the two hands. He is right-handed.

The next case, that of Samuel S., a man 31 years old, illustrates the fact that even very marked differences in the form of the radial pulse on the two sides, differences perfectly evident both to the finger and on the sphygmogram, may be associated with a comparatively small difference in the flow in the two hands. The right radial showed a typical pulse of aortic insufficiency with abrupt ascent to a sharp apex and abrupt fall, while the left radial gave a sphymogram with a rounded apex. The blood-pressure in the two brachials was also quite different, the systolic pressure being 157 in the right and 118 in the left. The physical signs of aortic insufficiency were present.

The blood-flow measurement showed a difference no greater than may be seen in normal persons between the two hands (11.11 grams per 100 c.c. per minute for the right and 10.32 grams for the left, with room temperature 22.2 C.), a perfectly normal flow for a man of this age. The conclusion was drawn that the aneurysm in distorting the form of the pulse-wave did not interfere materially with the free passage of blood through the left subclavian artery. The man died the same night about five hours after the examination by a rupture of the aneurysm into the left bronchus. It is worthy of remark that five hours before his death the blood-flow in his hands, which no doubt in this case was an index of the output of his heart, was quite normal. He was to die, not because his heart was failing, but because the wall of the aneurysmal sac had been thinned to the bursting point. A very different tale would have been told by the hand flow in a case of impending heart-failure as in Stephen F., or Albert H. (Paper X), or Anthony P.

Samuel S., a colored music teacher, aged 31, was admitted to the City Hospital Dec. 7, 1912, with thoracic aneurysm. He is a well-developed man 5 feet, 10½ inches tall, weight 160 pounds. He has had spells of intense dyspnea for the past six weeks. He has been continually getting worse to the present time, is much cyanosed, and suffers much from cough which he has had from the age of 16. He has smoked cigarettes to excess, and also has used a good deal of alcohol. He denies lues although he admits the possibility of it.

The left pupil is smaller than the right and does not react to light or accommodation. There is diffuse pulsation of the lower third of the neck. Tracheal tug is present. The left side of the thorax moves less than the right. The percussion note is dull over the entire left side [compression of the left lung by the aneurism(?)]. Over the left lung the breath-sounds are very faint, distant and bronchial in character. The cardiac dulness at the level of the second rib extends three fingers' breadth to the right of the right sternal border and the same distance to the left of the left sternal border. In the fourth interpsace it extends from two fingers' breadth to the right of the right sternal border to the left midaxillary line. The apex beat is visible and palpable in the sixth interspace, two fingers' breadth outside the nipple line. Systolic and presystolic thrills are palpable over the apex. Loud booming systolic and diastolic murmurs are heard at apex. Loud presystolic murmur followed by systolic murmur is heard over aortic and pulmonic areas. The sternum rises fully a half-inch with each systole. The radial pulse is regular, rhythmical, asymmetrical, the sphygmogram of the left radial having a rounded apex, and that of the right a sharp (aortic insufficiency) apex. The pulse is synchronous in the two radials and of good volume and tension. The difference in the form of the pulse-wave is very evident to the finger.

The blood-flow in the hand was measured Dec. 10, 1912. Hands in bath at 1:50 p. m., in calorimeters at 1:59½, and out of calorimeters at 2:13 p. m.

TABLE 10.—Calorimetric Measurements in Case of Samuel S.

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
1:59	31.40	31.43	....	2:07	32.11	32.13	22.25
2:00	31.435	31.49	22.4	2:08	32.195	32.20	....
2:01	31.55	31.58	22.4	2:09	32.27	32.265	22.2
2:02	31.64	31.68	....	2:10	32.35	32.36	22.1
2:03	31.74	31.78	22.3	2:11	32.395	32.42	....
2:04	31.85	31.88	....	2:12	32.47	32.465	22.3
2:05	31.94	31.95	....	2:13	32.53	32.53	....
2:06	32.01	32.055	22.3	2:41	32.17	32.17	....

Cooling of calorimeters in twenty-eight minutes, 0.36 degree. Volume of right hand 580 c.c., of left hand 603 c.c. Water equivalent of calorimeters with contents, R., 3,559; L., 3,577. Rectal temperature 38.4 C. Blood-pressure left arm, systolic 118, 58 (sound suddenly diminished); right arm, systolic 157, 61 (sound abruptly diminished). Another observation on the right arm gave identical results. Three days previously, according to another observer, the pressures were 160 (systolic), 45 (change of sound) in the right, and 130, 55 in the left brachial.

A necropsy was performed by Dr. A. A. Johnson, Pathologist at the City Hospital, to whom I am indebted for the following details. Heart, left ventricle dilated moderately, average thickness 16 to 18 mm. Other cavities normal. The segments of all the valves except the aortic are normal and the orifices are not dilated. The aortic ring in the formaldehyd-preserved specimen measured 8 cm. The aortic valve segments are slightly thickened and curled along their free edges. The openings of the coronary arteries are free and of the usual size. The aorta immediately above the aortic ring is smooth and free from thickening. Opening from the anterior aspect of the transverse arch is a large sacular aneurysm adherent to the sternum. The sac is oval, 10 by 8 cm. in diameter. The walls are thin (2 to 4 mm.) and are quite free from fibrin. The opening from the aorta into the sac measures 5 by 3.5 cm. The innominate opens by a somewhat dilated mouth posterior and external to the opening into the aneurysm and situated opposite the middle of the latter opening. The left common carotid and subclavian arteries come off from the aorta about 1 cm. beyond the upper border of the opening between the aorta and the aneurysm. Rupture in the sac on the inferior surface has irregular edges and measures 3 by 1 mm., leading into the left bronchus 1 cm. from the bifurcation.

It will be seen that there was no stenosis of the orifice of the left subclavian, but its origin was situated distal to the orifice of the aneurysmal sac, while the origin of the innominate was directly opposite the center of that orifice. The direction of the opening of the innominate was such that the blood coming from the heart would pass straight into it, all the more as the opening of the innominate was somewhat dilated. This would account for the abrupt rise in the sphygmographic curve and the high maximum pressure in the right arm. The sudden fall in the sphygmogram if partly due to actual regurgitation through the aortic orifice, was probably due still more to the effect of rapid expansion of the thin aneurysmal sac, which after closure of the aortic valve would still go on yielding and so exert a suction action, especially on the orifice of the innominate placed directly opposite it. On the other hand, the action of the large aneurysmal sac lying proximal to the left subclavian would be to damp the pulse-wave in that artery and delay the arrival of the crest. This would not necessarily affect the total flow, the pulsatory element in which is measured not by the absolute height of the crest, but by the area enclosed between the sphygmogram and the line of diastolic pressure.[5]

The last case included in the group of aneurysms (that of John McL.) is the only one which shows a notably small hand flow. It is placed in this group merely to emphasize the point that in drawing any general deductions from such measurements the proper classification of the cases is of great importance.

John McL., a plasterer, aged 50, height 5 feet, 11½ inches, was admitted to the City Hospital July 6, 1912, with general edema (in face, hands, arms, legs and feet), also cyanosis in the lips and fingers. He complains of "kidney trouble." He looks anemic. The heart shows an impure first sound at the apex. The aortic second is greatly accentuated, the blood-pressure is high (systolic 200). The abdomen is distended with free fluid. Albumin and casts were present in the urine all along. On July 11 about 7 liters of fluid was removed from the abdomen. There was no detectable fluid in the thoracic cavity. A diagnosis of hepatic cirrhosis was made. Aug. 19, 7,080 c.c. of fluid was removed from the abdomen.

On Aug. 27, 1912, the hand and foot flows were estimated and found exceedingly small (0.41 gram per 100 c.c. per minute for the right hand and 0.57 gram for the left hand, with room temperature 22.2 C.; 0.17 gram per 100 c.c. per minute for the right foot and 0.14 gram for the left foot, with room temperature 21.2 C.).

Aug. 28, 1912, 1,965 c.c. of liquid was taken from the abdominal cavity at 1:30 p. m., and the hand and foot flows were again measured. They were larger than on the previous day, but still quite small (1.11 grams per 100 c.c. per minute for a period of seventeen minutes for the right hand and 1.18 grams for the left hand, with room temperature 21.1 C.; 0.66 gram per 100 c.c. per minute for the right foot for the last ten minutes of a period beginning twenty minutes after insertion of the feet into the calorimeters, and 0.65 gram for the left foot). The ratio between the flows in the feet and hands (1:1.75) is near enough the normal to permit the conclusion that the small flow in both has a common cause. The presence of an aneurysm of the aorta was not diagnosed during life. The small blood-flow in the hands has certainly nothing to do with the existence of the aneurysm. It is without doubt dependent on the cardiorenal, or cardiorenalhepatic affection, that is to say, on such factors as the vasoconstriction of which the high blood-pressure is one expression, on the coincident anemia, and on the crippling of the heart muscle. The small flow in the feet may also depend in part on the mechanical hindrance imposed by the fluid in the peritoneal cavity or in the connective tissue of the legs. But if this were an important factor the ratio of hand to foot flow would be disturbed.

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[5] Paper V of this series, THE ARCHIVES INT. MED., 1912, ix, 706.

The patient died Dec. 27, 1912. The necropsy showed general peritonitis, aneurysm of the descending thoracic aorta, cloudy swelling and parenchymatous change in the kidneys. The pericardium was adherent to the left pleura, but not to the epicardium. The heart was pale (weight 300 grams), with some dilatation and hypertrophy of the left ventricle. The mitral orifice was dilated and the edges of the mitral valve were thickened and puckered. The edges of the aortic valve were thickened and slightly curled. The sinuses of Valsalva were dilated. Many sclerotic plaques were about the coronary openings. The right coronary vessels were not patent. The left coronary vessels were free but sclerosed. The aortic ring was much dilated, 10.5 cm. in circumference. The whole intima of the aorta was very much thickened. Here and there were areas of sclerosis. The openings of the large vessels were dilated. Eight centimeters beyond this there was an opening on the left posterior wall of the aorta 2 cm. in diameter, opening into a sac 4 cm. in diameter. The body of the fifth thoracic vertebra had been slightly eroded. Beyond this the thoracic aorta was much thickened in irregular areas. About 1,000 c.c. of straw-colored fluid was in the left pleural cavity. The abdomen contained about 10 liters of cloudy fluid with many shreds of fibrin. The visceral and the parietal peritoneum was dark in color and covered with exudate. The intestines were adherent. The liver showed no scarring; weight 1,660 grams. In the kidneys the cortex was not sharply differentiated from the medulla. The whole kidney was dark in appearance, with cloudy swelling to parenchymatous change. For these details I am obliged to Dr. A. A. Johnson.

III. MISCELLANEOUS VASCULAR CONDITIONS INCLUDING VASCULAR NEUROSES

Among these are three cases of Raynaud's disease.

Margaret H., aged 15, suffering from Raynaud's disease in the fingers, had a flow in the right hand of 5.33 grams per 100 c.c. of hand per minute and 6.67 grams in the left, with room temperature 23.6 C. The protocol has already been published.[6] The considerable inequality in the flow in the two hands is probably due to a functional vasomotor difference. When there are no anatomical reasons for such a difference in flow it either disappears at subsequent examinations or is reversed as regards the two hands. In cases in which a marked difference is obtained in the two hands in several examinations, the deficiency being always in the same hand and the ratio of the flows in the two hands not changing greatly, there is reason to believe, in the absence of obvious anatomical differences, that the difference in flow may depend on pathological changes in the thorax or in the arm or hand itself which have not yet definitely disclosed themselves by other symptoms.

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[6] Heart, 1911, iii, 79.

The flow in Margaret H. is distinctly subnormal, which corresponds with the fact that her hands were cold to the touch, although she did not have an attack during the examination. The relatively small flow may be related to the tendency to dyspnea which she states has existed for some years. The most striking result of the examination was the intense reflex vasoconstriction produced in the left hand when the right was put into cold water, the flow being reduced from 6.67 grams to 2.97 grams per 100 c.c. per minute. Although intense, the vasoconstriction was transient, lasting only for two minutes and then giving place to distinct vasodilatation, the flow increasing to 8.28 grams in the left hand, while the right continued in the cold water. Immersion of the right hand in warm water produced no further increase, but rather a decrease. The vasomotor mechanism of the hand seems, therefore, to respond with abnormal readiness to vasoconstrictor influences and with less than normal readiness to vasodilator influences. The short duration of the intense crossed reflex vasoconstriction relates the case to those of early peripheral neuritis,[7] and it is of interest, in this connection, that neuritic changes may be associated with the Raynaud's syndrome.

The second case of Raynaud's disease was that of Mrs. W. G., aged 28, who was seen April 24, 1911. About one and one-half years previously, after a sleigh ride, she noticed that the fingers of both hands became cold, "white like those of a dead person" and numb. Sometimes the fingers became purple. All the phalanges were involved. She feels sure they were not frost-bitten. Since that time she has had many attacks, each lasting usually five to ten minutes, but occasionally almost an hour. The attack generally begins in the thumb. Putting the hands into cold water does not necessarily bring on an attack. A cold full bath is more likely to do so. The thumbs are apt to become numb if she holds anything in her hands for any length of time. Long before this condition came on her arms and hands used to go to sleep a great deal even when she was not lying on them. Also for as long as she can remember small injuries to the skin of the hands or arms healed badly. She pointed out the scar of a small burn on the left hand which was still raised above the surface although otherwise healed. It was a most trifling burn she said. Even a little scratch leaves a scar. She showed various marks of old injuries on the arm. She has been fighting the condition by going out to walk without gloves, continuing to walk with her hands exposed even when they became numb, and thought that some time she improved it in this way, her hands afterwards becoming warm. Her general method has been to immerse them in warm water on coming in. The attacks are apt to be induced by a damp day, even if not cold. The hands to-day feel markedly cold to the touch, not only the fingers, but the hands midway to the wrists. The day was not cold and she was wearing kid gloves. Her arms are mottled with purple spots. She has no trouble in the feet, nose, or elsewhere. Her general health is satisfactory, but there is some shortness of breath on exertion. She is fat and well nourished, and the arms and hands are quite plump. She suffers much from nervousness.

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[7] Paper XII of this series.

The blood-flow in the hands was examined April 24, 1911. Pulse 108 (sitting). Mouth temperature 37.55 C. Hands put into bath at 10:10 a. m. At 10:15 it was seen that the left arm was getting purple; the right arm remained unchanged. She said the left hand felt colder than the right, and that the left arm and hand felt as if swollen. Hands put into calorimeters at 10:20 a. m.

TABLE 11.—Calorimetric Measurements in Case of Mrs. W. G.

Time	Right	Left	Notes
10:19	30.125	30.13	
10:24	30.11	30.13	
10:25	30.12	30.15	Room temp. 25.3 C.
10:27	30.17	30.19	
10:28	30.20	30.22	
10:29	30.22	30.24	
10:30	30.25	30.26	
10:31	30.26	30.26	
10:32	30.27	30.27	
10:33	30.29	30.31	
10:34	30.31	30.32	At 10.34 put left hand in water at 43 C.
10:35	30.33	.....	
10:36	30.36	.....	Room temp. 27 C. Face and ears red. She says the left hand feels swollen greatly.
10:37	30.38	.....	
10:38	30.40	.....	
10:39	30.42	.....	Room Temp. 25.3 C.
10:40	30.47	.....	
10:41	30.50	.....	
10:42	30.54	.....	
10:43	30.57		
10:44	30.60		
10:45	30.62		
10:46	30.67		Room temp. 24.9 C.
10:47	30.70		At 10:47 left hand put in water at 12 C.
10:48	30.71		
10:49	30.72		
10:50	30.73		
10:51	30.75		
10:52	30.77		
10:53	30.79		
10:54	30.81		At 10:54 dried and wrapped left hand. It is red and is not specially cold to touch. Room temp. 27.4 C.
10:55	30.83		
10:56	30.86		
10:57	30.89		
10:58	30.92		Hand out of calorimeter at 10:58.
10:59	.....		10:59 temp. of L. is 30.30 C.
11:24	30.74		11:24 temp. of L. is 30.06 C. Room temp. 25.8 C.

Cooling of calorimeters, R., 0.18 C. degree in twenty-six minutes; L., 0.14 degree in twenty-five minutes. Volume of right hand 391 c.c., of left hand 375 c.c. Water equivalent of calorimeters with contents, R., 3,408; L., 3,395. The left hand may be swollen a little, as her ring, which had been removed, now goes on with difficulty, yet the subjective feeling of extreme swelling which she had is obviously no index of the actual swelling.

The small initial flow in this patient (3.62 grams per 100 c.c. per minute for the right hand and 3.44 grams for the left, with the relatively high room temperature of 25.3 C.) is considerably more striking than in the case of Margaret H. This agrees well with the longer duration and greater development of the condition in Mrs. W. G. Immersion of the left hand in warm water caused a fair and persistent increase in the flow in the right (to 5.16 grams), although the absolute flow was still small. Subsequent immersion of the left hand in cold water caused a strong vasoconstriction in the right hand, diminution of the flow to 2.46 grams per 100 c.c. per minute for the first three minutes and 3.93 grams for the last four minutes. Although the temperature of the cold water was purposely made higher than usual (12 C. instead of 8 C.), she complained greatly of the cold and withdrew her hand intermittently. This was seen also in the other cases, and the hypersensitiveness of the afferent receptors to cold as gauged by the sensation elicited has its parallel in their hypersensitiveness to cold as components of the reflex vasomotor arc.

The third case of Raynaud's disease (Mrs. C. B.) illustrates the condition when it has existed for a long time and has gone on to gangrene. The age of the patient was 29. Not only was the local condition more severe than in the last case, but the general physical condition was worse. The hand flow for a period of sixteen minutes before the vasomotor reaction was tested was 3.23 grams per 100 c.c. per minute for the right hand and 4.29 grams for the left. For the last six minutes of this period the flows worked out at 3.65 grams and 3.80 grams for the right and left hands, respectively. The reflex reaction to warmth was fair (the flow in the right hand increasing for the first two minutes of immersion of the left in warm water to 6.55 grams per 100 c.c. per minute), but it was transient, and for the last ten minutes of the period the flow was only 4.30 grams per 100 c.c. per minute. The reflex reaction to cold was also anomalous, possibly because of the existence at this stage of the disease of considerable anatomical changes in the vessel.

Mrs. C. B., aged 24, was admitted to the Lakeside Dispensary June 1, 1908, suffering from Raynaud's disease. She was treated with nitroglycerin without benefit. April 23, 1913, on account of coughs, sweats, and general weakness she was referred to the Medical Department of the Dispensary when the following data were elicited. Both hands are affected. The condition was first noted one day in winter seven years ago, the fingers becoming cold and pale and then getting purple. The attacks have been growing steadily worse, especially in the last five years. Sometimes small grangrenous areas form quickly at the ends of the fingers and quickly recover, but always with some loss of substance, so that the terminal phalanges of several of the fingers have lost a considerable proportion of their length and most of them have lost their nails. On all the fingers the nails are atrophic. She has considerable pain in the fingers when they "break out." She has had pain and marked stiffness in the right wrist and right forearm for about two years, and she uses the right hand but little on account of the stiffness of the wrist. The skin of the right forearm is somewhat stretched and distinctly glossy in comparison with that of the left. She cannot bear to put her hands into cold water. She has no such symptoms in her feet, nose or elsewhere. Some years ago she had a sore on her ankle, due, as she thinks, to a habit of kicking the ankle with the other foot. The sore refused to heal and she was put in hospital for several weeks, during which time her general health and strength improved greatly, and the sore also improved, although it took a long time before it was healed. She is pale and thin. There is some pigmentation of the skin and some dulness at the apex of the left lung. The radial pulse is small.

Examination of the blood-flow in the hands was made May 9, 1913. The marked pallor with some lividity and the "stone cold" feeling of the hands, especially of the fingers, was striking, although she was wearing gloves. The day was rather chilly. The terminal phalanx of one finger of the right hand had a small sore on the point of it which she said caused her some pain. Pulse (sitting) 112, weak. Hands in bath at 3:15 p. m., in calorimeters at 3:27. Mouth temperature, 37.35 C.

TABLE 12.—Calorimetric Measurements in Case of Mrs. C. B.

Time	Right	Left	Room Temp. C.	Time	Right	Notes
3:26	31.18	31.17	.....	3:53	31.135	3:52 left hand put in water at 43 C.
3:28	31.09	31.13	.....	3:54	31.155	Room 22.8.
3:29	31.09	31.13	21.3	3:55	31.16	
3:30	31.08	31.12	.....	3:56	31.17	Room temp. 22.9 C.
3:31	31.08	31.12	21.5	3:57	31.175	
3:32	31.08	31.11	.....	3:58	31.18	
3:33	31.085	31.11	.....	3:59	31.195	Room temp. 22.95 C.
3:34	31.08	31.11	21.8	4:00	31.20	
3:35	31.08	31.11	.....	4:01	31.20	
3:36	31.08	31.115	.....	4:02	31.205	
3:37	31.085	31.12	22.0	4:03	31.21	
3:38	31.085	31.12	.....	4:04	31.225	At 4:04 left hand put in water at 12 C.
3:39	31.085	31.125	.....	4:05	31.24	She feels it very cold. Left hand taken out of water intermittently.
3:40	31.09	31.14	.....	4:06	31.25	
3:41	31.085	31.15	22.1	4:07	31.255	Room temp. 22.7 C.
3:42	31.09	31.16	.....	4:08	31.26	The cold water is now at 13.5 C. The left hand is red. She says if it had not first been in warm water it would have been purple in the cold water. To the touch the left wrist is warm (vasodilatation), much warmer than the right.
3:43	31.09	31.17	.....	4:09	31.27	
3:44	31.09	31.18	.....	4:10	31.28	
3:45	31.09	31.195	.....	4:11	31.295	
3:46	31.095	31.20	22.0	4:12	31.305	
3:47	31.10	31.205	.....	4:13	31.34	4:13 hand out calorimeter.
3:48	31.10	31.21	.....	4:43	30.96	4:43 temp. L. 30.58 C.
3:49	31.105	31.215	.....			
3:50	31.115	31.22	22.6			
3:51	31.12	31.225	.....			
3:52	31.12	31.23	.....			

Cooling of calorimeters, R., 0.38 C. in 30 minutes; L., 0.65 C. in 51 minutes. Volume of right hand 273 c.c., of left 282 c.c. She is right handed. Water equivalent of calorimeters with contents, R., 3.313; L., 3.320.

It may be noted that in these three cases of Raynaud's disease there was evidence that a coexisting or preexisting general feebleness of the circulation conspired with the local condition in producing the symptoms. The blood-flow measurements suggested that if the general circulatory conditions had been normal the local tendency to vasoconstriction might not have sufficed to reduce the flow to the level at which the symptoms became obtrusive. This was the suggestion merely derived from the three cases studied and it is not claimed that it has a general application. At any rate since hand flows habitually as small or smaller are often encountered in cases which never develop Raynaud's disease, the primary factor must be a tendency, whatever its essential cause, to the local diminution in the flow.

In a case of "dead fingers" in an elderly man affecting only the right hand, the flows were among the smallest observed in the whole investigation, and this not only in the hand obviously affected, but also in the other. The patient had been sitting in a well-warmed room for an hour before the examination, yet the calculated flow for the right hand was only 0.09 gram per 100 c.c. per minute and for the left 0.25 gram, with room temperature 20.5 C. A fair reflex vasodilatation was obtained in the right hand on the immersion of the left in warm water, the flow increasing to 0.5 gram, still of course a very small flow, but relatively a great increase. The dead condition of the right hand is therefore probably not due to anatomical change in the vessels, but to a vasoconstriction.

The next case in this group is that of Maurice T., a man 41 years old, who had lost a leg through obliterative arteritis.

Maurice T., a tailor's cutter, height 5 feet 7 inches, weight about 175 pounds, a well-built man, apparently in perfect health. He was seen April 17, 1911. About eight years ago in winter he began to feel the toes of the left foot cold. The little toe was first affected; gradually the same condition came on in the other toes. After awhile the toes became painful also. The whole foot became involved by degrees. Then cramp-like pains began to trouble him in the calf of the left leg. The trouble was worse in winter. Small nodules on the foot and toes became gangrenous. Eventually, four years ago, the left leg had to be amputated above the knee. The arteries were found extensively affected. He never had any pain above the knee. About six months ago he noticed that the little toe of his right foot was cold. Later on it began to pain him. Now the whole right foot is cold to the touch and the pulse in the dorsalis pedis poor. The little toe has a raw surface where it is contact with the next toe and the nail is apparently going to come off. He knows of no injury to it. The pain in the foot is so great that while he is in bed he cannot sleep. When he stands the pain disappears, but he has pain also when he walks. The arch of the right foot is broken down and he has to wear a support in his shoe. There is hyperidrosis of the foot in spite of the fact that it is cold. The flow in the hands was examined April 17, 1911. Mouth temperature 36.5 C. Hands put into bath at 10:05 a. m. and into calorimeters at 10:18. Pulse (sitting), 92.

At this time the foot calorimeters had not been constructed so that only an examination of the flow in the hands was made. This was done with the idea that some information of possible value for a prognosis in regard to the leg condition might be obtained, (1) from the absolute amount of the hand flow as an index of the flow in the periphery in general, (2) from the nature of the reflex vasomotor response as an index of the existence of a tendency to vasomotor spasm, a functional condition which there is good reason to believe may underlie or at least precede in certain cases the development of obliterative arteritis. The flow in the right hand was 4.87 grams per 100 c.c. per minute and in the left 6.67 grams, with room temperature 25.7 C., a distinctly subnormal flow. Immersion of the right hand in cold water caused one of the most intense reflex vasoconstrictions in the contra-lateral hand which has been witnessed in the whole course of these observations, the flow declining to 2.59 grams per 100 c.c. per minute for the first five minutes and only reaching 5.59 grams after a further immersion in the cold water of four minutes. The reflex to warmth is also well marked, the flow in the left hand eventually rising to 10.96 grams. The general indication of the observations as regards the question propounded was that a vasomotor instability with a tendency to excessive vasoconstriction in the extremities might be the basis for the symptoms in the foot. The inequality in the flows in the two hands corroborates the idea of some degree of vasomotor abnormality. Anatomical changes in the nerves were of course not excluded. Unfortunately, the man soon after removed to a distant part

TABLE 13.—Calorimetric Measurements in Case of Maurice T.

Time.	Right	Left	Notes.
10:17½	29.57	29.58	
10:20	29.58	29.60	
10:21	29.60	29.62	
10:22	29.62	29.65	Room temperaature 25.7 C.
10:23	29.66	29.70	
10:24	29.70	29.76	
10:25	29.74	29.82	
10:26	29.78	29.86	Room temperature 25.6 C.
10:27	29.81	29.92	
10:28	29.85	29.97	Room temperaature, 26 C. Ears red.
10:29	29.89	30.02	
10:29½	....	....	Right hand put in water at 9 C.
10:30	....	30.08	
10:31	....	30 09	
10:32	....	30.11	The cold water is now 10.6 C.
10:33	....	30.12	He feels the cold water extremely.
10:34	....	30.14	Room temperature 26. 6 C.
10:35	....	30.15	
10:36	....	30.19	
10:37	....	30.22	
10:38		30.24	Room temperaature 25.5 C.
10:39		30.29	At 10:39 put right hand in water at 43°.
10:40		30.31	
10:41		30.34	Room temperature 25.0 C.
10:4–		30.38	Room temperature 25.1 C.
10:43		30.45	
10:44		30.52	Room temperature 25.2 C.
10:45		30.60	Ears still red.
10:46		30.65	
10:47		30.72	Room temperature 25.2 C.
10:48		30.80	At 10:48 dried and wrapped right hand.
10:49		30.82	
10:50		30.88	Room temperature 25.2 C.
10:51		30.94	
10:52		31.00	Room temperature 25.3. C.
10:53		31.07	
10:54		31.13	Hand out of cal.
11:09		....	Temp. of room 29.65 C.
11:09½		31.01	

Volume of right hand, 470 c.c.; of left hand, 466 c.c. He is right-handed.

of the country, and up to the present it has not proved possible to learn the further history of the case.

In the case of Anthony P., a man 36 years old, with gangrene of the fingers and toes, the question arose whether the condition depended on a vasomotor neurosis.

Anthony P., a Polish laborer, aged 36 years, height 5 feet 8 inches, weight 150 pounds, was admitted to City Hospital, Oct. 9, 1912, complaining of sore fingers and toes. He froze his feet last winter. There is no history of frost-bite of the fingers. He had numbness of the fingers a year ago. Owing to the condition of his fingers he was forced to quit work about three weeks before admission. On admission the right hand showed beginning gangrene at the tip of the thumb, loss of the distal half of the nail of the middle finger, the remainder being undermined and loss of the entire nail of the ring-finger. The left hand showed purplish discoloration of the thumb, the nail being absent, loss of the entire nail of the index finger except the root, and gangrene about the base of the nail of the ring-finger.

A blood-flow examination of the hands was made on Oct. 11, 1912, with a very warm day (room temperature 27.8 C.). The flow came out only 1.22 grams for the right hand, and 1.12 grams for the left per 100 c.c. per minute, or allowing for the swelling of the left hand, 1.27 grams. The pulse-rate was 120 (sitting). The conclusion drawn was that if the small flow depended solely on the local conditions it was unlikely that the constriction of the vessels was purely functional, since the high room temperature would have caused vasodilatation. He was in such poor condition that a sufficient examination of the vasomotor reflexes was postponed. In the meantime cyanosis of the face and dilatation of the neck veins became prominent and physical examination revealed the signs of serious involvement of the heart (mitral stenosis, aortic insufficiency and signs of impairment of the myocardium). It was no longer possible to draw deductions from the small hand flow, and the slight response to the high external temperature as to the condition of the local circulation, since the state of the heart itself was sufficient to account for the small flow even provided that the cutaneous vasodilatation was the maximum possible with so small a driving power. Also fever (his rectal temperature was 39.65 C.) is associated with cutaneous vasoconstriction and a small hand and foot flow.[8] Had the feet been normal, a comparison of the hand and foot flow might still have yielded information, since the cardiac insufficiency might be expected to diminish the flow in both without affecting the normal ratio between the hand and foot flow, whereas a vascular constriction (vasomotor or anatomical) confined to the hands would be revealed by a disturbance of this ratio in favor of the feet. The local conditions, however, soon became a matter of indifference in view of the serious involvement of the heart. The patient died October 12.

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[8] Stewart, G. N.: Paper VIII, Jour. Exper. Med., 1913, xviii, 372.

The necropsy showed the following: Left lung: infarct in the lower lobe 5 cm. in diameter. Right lung: infarct in upper lobe 2½ cm. in diameter, and in lower lobe 5 cm. in diameter. Heart engorged on the right side and left side dilated: heart-muscle dark and flabby. The pericardium contains 100 c.c. of fluid. Aortic valve, left cusp hardened and shortened. Mitral admits tip of index-finger. Vegetations about the valves. Tricuspid, edges of valves thickened, recent vegetations. Liver, 1,800 grams, with chronic passive congestion. Spleen, weight 140 grams, chronic passive congestion. The kidneys show much arterial thickening. Blood-vessels: radial, practically no arterial thickening. The fingers show stasis of blood in the vessels. A cross-section of the index-finger shows much perivascular infiltration, but no thickening of the vessel walls. Pathological diagnosis, septic endocarditis.—(From Dr. Johnson's report.)

In a case of diabetic gangrene of the feet in a man 63 years old, the flow with a room temperature of 25.6 C. was 1.39 grams for the right foot and 1.83 grams for the left, or allowing for the swelling of the latter 1.95 grams. An interesting point is that the flow in the foot in which the gangrene had made most progress was greater than in the other foot. There is scarcely any question that this is due to inflammatory reaction. The diminished flow in the toes actually involved, if the flow is diminished there, would not show in a measurement of the flow through the whole foot. The sum of the flows in the feet, although subnormal, is not strikingly deficient, and the ratio of foot to hand flow (1:1.85) falls within the normal range. The hand flow was measured on the day preceding the observations on the foot and came out 2.65 grams for the right hand and 3.32 grams for the left per 100 c.c. per minute, with room temperature 22.0 C. In hospital cases presenting no rapid clinical changes, our experience has shown that such observations can safely be compared. The fact that the flow both in the hands and feet is decidedly below the normal agrees with the well-known feebleness of the cutaneous circulation in diabetes, and is probably in part due to cardiac changes. The vasomotor reflex, when warm water is applied to the contralateral hand, is very poor. Whether this indicates the beginning of pathological changes in the hand arteries also cannot of course be definitely stated. It is in any case interesting to correlate the enfeeblement of this vasomotor reflex with the enfeeblement or disappearance of skeletal reflexes such as the knee-jerk, which is known to occur in long-standing cases.

James P., a teamster 63 years old, was admitted to the City Hospital, Aug. 16, 1911, with a small ulcer on the inner surface of the left great toe and a scar in the same position on the right great toe. He came for treatment for his foot. It was found that the urine contained 4 per cent. of sugar with a trace of albumin. He was put on a diabetic diet. The blood-count showed erythrocytes 4,890,000, leukocytes 7,800, hemoglobin 90 per cent. April 28, 1912, the percentage of sugar in the urine was reduced to 0.8. April 11, 1912, when the blood-flow in the feet was examined there were small necrotic areas on the great and second toes of the right foot. The distal half of the left foot was bluish-red and the foot considerably swollen. The toes of the right foot were also bluish-red. He says that sometimes the left foot is hot, but when the flow in the feet was examined this was not the case.

Feet in bath at 1:21 p. m.; in calorimeters at 1:33, and out of calorimeters at 2:00; 3,740 c.c. of water in each calorimeter.[9]

Mouth temperature 37.45 C. Pulse (sitting), 68.

TABLE 14.—CALORIMETRIC MEASUREMENTS IN CASE OF JAMES P.

Time.	Right	Left	Room Temp. C.	Time.	Right	Left	Room Temp. C.
1:37	30.82	30.76	....	1:51	30.995	30.97	....
1:38	30.82	30.80	25.9	1:52	30.98	31.00	....
1:39	30.86	30.82	....	1:53	31.01	31.01	25.4
1:40	30.875	30.83	....	1:54	31.02	31.025	....
1:41	30.885	30.84	....	1:55	31.03	31.04	....
1:42	30.885	30.855	25.8	1:56	31.035	31.05	....
1:43	30.905	30.87	....	1:57	31.05	31.06	....
1:44	30.92	30.88	....	1:58	31.05	31.08	....
1:45	30.935	30.915	....	1:59	31.06	31.10	....
1:46	30.94	30.92	....	2:00	31.02	31.09	25.4
1:47	30.95	30.935	....	2:28	30.76	.....	....
1:48	30.96	30.95	25.2	2:29	.....	30.75	....
1:49	30.975	30.96	....	2:32	30.71*	.....	....
1:50	30.98	30.96	....	2:33	......	30.72*	....

* After better stirring.

Cooling of calorimeters, R., 0.31 degree in thirty-two minutes, L., 0.37 degree in thirty-three minutes. Volume of right foot in calorimeter 1,090 c.c. of left foot 1,175 c.c. Rectal temperature (taken by himself and doubtless too low as compared with mouth temperature), 37.5 C. Water equivalent of calorimeters with contents, R., 4,760, L., 4,820.

The next case is remarkable for the fact that the flow in the hands per 100 c.c. per minute was very much less than in the feet, a quite unusual circumstance.

K., a laborer aged 50, was admitted April 15, 1912, to the City Hospital. He was much cyanosed on admission, and when the flow in the hands was first examined next day the cyanosis was still well marked in the face, nose, ears and hands, although less pronounced than on admission. There is gangrene of the toes on left foot. The pulse can be felt in the dorsalis pedis. Blood-pressure 140 systolic, 100 diastolic. He had some cough and râles of every description were heard all over the lungs. The fingers were markedly clubbed. The heart-sounds were weak. A soft systolic murmur and reduplicated second sound were heard over the left sternal border, more marked at the base. The heart was enlarged. The pulse at the wrist is not strong, but by no means so weak as to suggest that the blood-flow in the hands would be found so small as is actually the case.

April 16 the flow in the right hand came out only 0.27 gram per 100 c.c. per minute and in the left hand 0.28 gram, for a period of eighteen minutes in the calorimeters, with room temperature 23.8 C. Immersion of the left hand in warm water caused no increase whatever in the flow in the right. The very small flow in the hands agreed with the diagnosis of myocarditis. It is possible also that a factor in the small flow was nervousness, as this was the first examination, and the patient was a foreigner, speaking no English. Still the effect of nervousness on the flow usually passes away more quickly.

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[9] For the details of measurements of foot-flow see Paper VII of this series, Jour. Exper. Med., 1913, xviii, 354.

April 18 he was again examined. The cyanosis was now much diminished and the radial pulse was stronger. The flow in the right hand was 1.05 grams and in the left 1.43 grams per 100 c.c. per minute, with room temperature 22.5 C., still quite a small flow, although much greater than at the last examination. In the right foot the flow was 2.15 grams per 100 c.c. per minute, and in the left foot 3.42 grams. Immersion of the right foot in cold water was accompanied by a reduction in the flow in the left foot to 2.68 grams, which was only slightly increased (to 2.87 grams) when the right foot was put into warm water.

Feet in bath at 2:07 p. m., in calorimeters 2:19 p. m. Patient sitting. 3.740 c.c. water in each calorimeter. At 2:45 p. m. the right foot was put into water at 10.5 C.

TABLE 15.—Calorimetric Measurements in Case of K.

Time	Right	Left	Room Temp. C.	Time	Left	Notes
2:22	29.99	29.93	.....	2:46	30.605	
2:23	30.00	29.95	20.5	2:47	30.625	
2:24	30.02	29.99	.....	2:48	30.635	Room temp. 20.7 C.
2:25	30.03	30.05	.....	2:49	30.655	
2:26	30.045	30.08	.....	2:50	30.665	
2:27	30.07	30.125	.....	2:51	30.70	
2:28	30.08	30.14	20.4	2:52	30.715	
2:29	30.09	30.175	.....	2:53	30.725	
2:30	30.10	30.22	.....	2:54	30.745	At 2:54 right foot put in water at 42.8 C.
2:31	30.11	30.245	.....			
2:32	30.125	30.275	.....	2:55	30.76	Room temp., 21.0 C.
2:33	30.135	30.30	.....	2:56	30.775	Right big toe painful.
2:34	30.145	30.33	.....	2:57	30.80	
2:35	30.17	30.35	20.1	2:58	30.825	
2:36	30.19	30.38	.....	2:59	30.835	
2:38	30.21	30.42	.....	3:00	30.85	
2:39	30.22	30.46	.....	3:01	30.87	
2:40	30.23	30.47	.....	3:02	30.90	Room temp. 21.3 C.
2:41	30.23	30.50	.....	3:03	30.925	
2:42	30.235	30.52	.....	3:04	30.935	
2:43	30.24	30.535	....	3:05	30.94	Foot out of calorimeter.
2:44	30.26	30.56	.....	3:17	30.75	Room temp. 20.9 C.
2:45	30.275	30.595	.....	3:18	.....	Temp. of R. is now 29.79 C.

Cooling of calorimeters, R., 0.485 C. in thirty-three minutes; L., 0.19 C. in twelve minutes. Rectal temperature 37.6 C. Volume of right foot in calorimeter 950 c.c., of left 985 c.c. Water equivalent of calorimeters with contents, R., 4,652; L., 4,679.

The question whether the gangrene was going to spread was what chiefly interested the physician in charge of the case. The fact that the flow in the feet was so good was interpreted as favorable for the prognosis, although of course it was impossible to say to what extent the flow in the toes themselves had been interfered with. The left foot was somewhat swollen, as shown by the volume measurement. Yet it was only a little over 3 per cent. larger than the right. The greater flow in the left was probably related to a certain degree of inflammatory reaction. The foot soon began to heal up. But on April 25 the temperature, which had hitherto never surpassed 100 F., began to rise, reaching 104.2 F. on April 27. Then it fell and remained below 100 F. till his death on May 3.

The existence of a relatively good flow in the feet associated with a poor flow in the hands demands some further remark. It is probable that the immediate cause of the lesion in the left foot was exposure to cold. If so, it is likely that the already existing feebleness of the circulation and the poor response of the vasomotor regulatory mechanism were contributing causes. Very likely both feet suffered injury, although it only went on to gangrene in the left. The flow in both feet may, therefore, have been increased by the reaction to the injury caused by the freezing, and this in spite of the feeble driving-power of the heart. Thus the flow in the feet may have been brought up by the accident of the inflammation approximately to the normal flow, while that in the hands fell far below the normal.

Miss W., aged 25, weight 128 pounds, has lost fourteen pounds since her illness began. She first noticed pain in the ankles with some swelling in March, 1908. The pain increases as the day goes on, and at about 7 p. m. it is worse but on lying down she gets relief. In the morning her eyes are swollen. The wrists also swell when she works much with her arms. There is some shortness of breath. She must lie down some part of the day if she desires to sit up at night, even to 9 o'clock. An eruption consisting of raised red spots comes out periodically on the legs, also, though much less copiously, on the arms. There is burning pain and itching in the spots. In a day they get brownish, and in two days have disappeared to a great extent, except that a brown stain persists for weeks. Several spots 2 cm. in diameter which had come out the previous day on her legs were examined. The reddish color did not diminish on pressure. From her description the spots resemble urticaria at first and then hemorrhage takes place into the wheals. On the trunk also are spots which she describes as wheals, which itch and are painful, but the most purpuric-looking spots are on the legs. On the front of each tibia is a spot with a blackish crust from which she says some matter came out, but generally no liquid escapes from them. Her feet and toes are cold and so are her hands, especially the terminal phalanges of the fingers. Her nails grow irregularly, probably more quickly than before, and are ridged. There is distinct defect of sensation in the toes and the adjacent parts of the foot. A pin-prick is scarcely felt, and then only as contact. She does not feel any tickling sensation when the sole is stroked and there is no plantar reflex. Good knee-jerks can be obtained. There is a long reddish scar on the back of one finger of the left hand. She says she had "blood-poisoning" some time ago in a small wound caused by a tack and healing did not occur for eighteen weeks. The heart-sounds are clear and unaccompanied by murmurs. The urine contains no albumin, casts or sugar. Her eye-sight is not affected.

The blood-flow in the hands was examined May 9, 1911. Pulse 88. Mouth temperature 37.6 C. Hands put into bath at 10:14½ p. m., and into calorimeters at 10:24.

TABLE 16.—Calorimetric Measurements in Case of Miss W.

Time.	Right	Left	Notes.
10:23	30.13	30.08	Room tempera- 24.0 C.
10:25	30.11	30.06	
10:26	30.10	30.05	
10:27	30.11	30.05	
10:28	30.09	30.04	
10:29	30.10	30.04	Room tempera- 24.1 C.
10:30	30.10	30.04	
10:31	30.10	30.03	
10:32	30.12	30.04	
10:33	30.12	30.035	
10:34	30.125	30.04	
10:35	30.13	30.045	
10:36	30.145	30.06	
10:37	30.16	30.06	At 10:37 left hand put in water at 43 C.
10:38	30.165	......	Room temperature 24.3 C.
10:39	30.17	......	Left hand is fairly red and the veins of fair size.
10:40	30.17	......	
10:41	30.18	......	
10:42	30.185	......	
10:43	30.195		Room temperature 24.3 C.
10:44	30.20		
10:45	30.215		At 10:45 left hand put in water at 9.1 C.
10:46	30.215		She feels left hand very uncomfortable.
10:47	30.22		
10:48	30.225		Room tempera- 24.3 C.
10:49	30.225		
10:50	30.23		
10:51	30.23		
10:52	30.235		Room temperature 24.4 C. At 10:52 dried and wrapped left hand. It is pretty red.
10:53	30.235		
10:54	30.24		
10:55	30.245		Room temperaature 24.5 C.
10:56	30.245		Hand out of calorimeter. Feels pins needles in it.
10:56½	......		Temperature of L., 29.91 (at 10:56½).
11:26	30.03		

Cooling of calorimeters, R., 0.215 C. in thirty minutes, L., 0.15 C. in nineteen and one-half minutes. Volume of right hand in calorimeter 292 c.c. of left 298 c.c. She is right-handed.

May 25, 1911, the physician in charge of the case reported that since the time of the blood-flow examination she had had rather severe intestinal symptoms and that her temperature rose to 103 F. He gave her calcium chlorid and alkalies. She is now much better than for a while and the spots have disappeared.

The flow in the right hand was 2.16 grams per 100 c.c. per minute, in the left 1.64 grams, with room temperature 24.1 C., a very poor flow for her age. Reflex vasodilatation is absent, or quite feeble, the flow in the right hand only rising to 2.38 grams when the left was immersed in warm water. Scraping the skin with a blunt point caused no local vasodilatation. Although the initial flow was so small a further reflex vasoconstriction, reducing the flow in the right hand to 1.72 grams, was obtained when the left hand was put into cold water. No doubt the coexisting anemia is a factor in reducing the flow through the hands. The toxemia (rheumatic perhaps) on which the purpura depends may also depress the flow more directly, either by enfeebling the heart or by vasoconstriction. The conclusion deduced from the blood-flow measurements was that the feeble cutaneous flow might be a factor in the condition, and that so far as this went, the indication was that such measures should be adopted as would increase the flow in the skin, including the treatment of such anemia as was present.[10]

The last case to be described in this paper is that of Charles H.

Charles H., a clerk 42 years old, height 5 feet 10½ inches, weight 140 pounds, was admitted to the City Hospital Nov. 23, 1912, with edema of the right foot and leg. The swelling began a month ago, commencing at the toes with inflammation, he says, resembling erysipelas. A little over a year ago he accidentally injured the right lower leg by a blow with a hammer about midway between knee and ankle over the tibia. It healed at the time. Afterward a sore opened from which matter was discharged. He entered a hospital, where the leg soon healed. He has pain as soon as he commences to walk. When he stands up for a few minutes the foot becomes very blue and the small blood-vessels distend. The swelling comes on with great rapidity (in ten or fifteen minutes) when he goes about on his feet, and disappears completely when he lies down for a little while. There are no varicose veins. He does not appreciate warmth or cold, or contact (blunt-point) on the dorsum of the right foot or on the lower third of the right leg. A pin-prick is felt as dull contact. There is no anesthesia above the level of the scar due to the injury, except for a small tongue just above and continuous with the scar. The right sole is very sensitive. It began to be hypersensitive just after the foot commenced to swell. When he awakes in the morning he has a burning sensation about the toe-nails of the right foot. This disappears when he walks about a little. When he stood up it was seen that his right leg became very red in the anesthetic region. On pressure the red color disappeared. He says that when he first came into the hospital the white spot produced on pressure remained for some time, but now it quickly becomes red again. When he first came into the hospital

TABLE 17.—CALORIMETRIC MEASUREMENTS IN CASE OF CHARLES H. FIRST EXAMINATION

Time	Right	Left	Room Temp. C.	Time	Right	Left	Room Temp. C.
3:26	31.43	31.43	....	3:51	31.15	31.165	....
3:29	31.36	31.31	22.7	3:53	31.135	31.18	23.0
3:31	31.33	31.26	....	3:55	31.125	31.185	23.1
3:33	31.305	31.24	22.8	3:57	31.12	31.19	23.15
3:35	31.28	31.23	23.1	3:59	31.105	31.21	23.1
3:37	31.26	31.195	23.15	4:01	31.09	31.225	....
3:39	31.235	31.18	....	4:03	31.08	31.24	23.0
3:41	31.22	31.17	23.1	4:05	31.07	31.24	....
3:43	31.20	31.16	....	4:07	31.06	31.245	23.0
3:45	31.18	31.155	23.1	4:10	31.01	31.18	....
3:47	31.17	31.155	23.0	4:21	30.865	31.04	....
3:49	31.16	31.15	....	....	.....	.....	....

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[10] Paper VI of this series, Jour. Exper. Med., 1913, xviii, 13.

the red color which came on when standing soon became pale blue, whereas after a fortnight in the hospital it remains red. The legs, however, continue to be cold to the touch. He would not know his leg and foot were becoming red if he did not see it. He says he cannot keep the right foot warm. When the left foot is sweating under the bedclothes and he puts his hand down to feel the right foot it is always cold. He looks anemic and feels pretty weak, though his appetite is good. He has lost nearly 30 pounds in weight since he had malaria in Texas three years ago. The knee-jerks and ankle-jerks are somewhat exaggerated, but there is no patellar or ankle clonus. Examination of the heart and lungs is negative in result and the heart sounds are clear though very weak and distant. The pulse is regular.

The flow in the feet was examined Dec. 5, 1912, the patient sitting. Feet in bath at 3:15 p. m., in calorimeters at 3:28, and out of calorimeters at 4:07; 2,775 c.c. of water in each calorimeter. (Table 17.)

Cooling of calorimeters in eleven minutes, R., 0.145 degree; L., 0.14 degree. Volume of right foot 961 c.c., of left 924 c.c. He has small feet (No. 7 shoes). Rectal temperature 37.6 C. Pulse (sitting) 100. Water equivalent of calorimeters with contents, R., 3,696, L., 3,668.

Second examination Dec. 10, 1912. Pulse (sitting) 96. Hands in bath at 3:14 p. m., in calorimeters at 3:27. At 3:40 right hand put into water at 42.8 C.

When taken out of the cold water the right hand was distinctly redder than the left. Cooling of calorimeters, R., 0.505 C. in forty-one minutes; L., 0.19 C. degree in sixteen minutes. Volume of right hand in calorimeter 367 c.c., of left hand 355 c.c. He is right-handed. Rectal temperature 37.35 C. Blood-pressure in right arm, systolic 108, 88 (sudden change in sound), 81 (sound gone). The left arm, systolic 108. (Table 18.)

TABLE 18.—Calorimetric Measurements in Case of Charles H. Second Examination

Time	Right	Left	Room Temp. C.	Time	Left	Room Temp. C.	Notes
3:26	31.89	31.85	21.9	3:47	31.90	22.5	
3:28	31.85	31.81	22.0	3:48	31.91	22.4	
3:29	31.85	31.81	22.15	3:49	31.92	....	
3:30	31.85	31.81	22.15	3:50	31.925	22.8	
3:31	31.855	31.82	....	3:51	31.93	....	
3:32	31.86	31.825	22.4	3:52	31.935	22.9	
3:33	31.865	31.83	22.6	3:53	31.94	....	
3:34	31.87	31.84	22.8	3:54	31.945	22.7	
3:35	31.875	31.84	....	3:55	31.955	....	At 3:55 right hand put in water at 8.6 C.
3:36	31.88	31.85	22.6	3:56	31.955	....	
3:37	31.88	31.855	22.5	3:57	31.955	....	
3:38	31.895	31.86	....	3:58	31.955	....	The right hand is red. He feels the water very cold.
3:39	31.895	31.86	....	3:59	31.95	23.7	
3:40	31.895	31.865	....	4:00	31.945	....	
3:41	.....	31.875	23.0	4:01	31.94	23.5	
3:42	.....	31.875	....	4:02	31.94	....	The right hand does not now feel cold at all. Still red.
3:43	.....	31.875	22.8	4:03	31.94	....	
3:44	.....	31.88	....	4:04	31.935	23.7	
3:45	.....	31.885	22.7	4:05	31.93	....	Hand out of calor. at 4:05.
3:46	.....	31.89	....	4:21	31.74	....	4:21 temp. of R. is 31.39 C.

The distribution of the anesthesia and the history of the case seem to indicate that a nerve injury was the starting point of the vascular condition. The flow in the right foot was 0.51 gram per 100 c.c. per minute and in the left 1.35 grams, with room temperature 23.0 C. The flow in the right hand was 3.43 grams, and in the left hand 3.71 grams per 100 c.c. per minute, with room temperature 22.6 C. While, then, the flow in the hands is much below the normal, which corresponds well with the rather feeble action of the heart and with the patient's anemic condition, the flow in the left foot preserves a ratio to that in the hands not far from normal. The flow in the right foot, however, is distinctly poor, even in proportion to the poor hand flow. The cause accordingly of the small flow in the right foot is not a central one, but is local. This agrees well with the patient's observation that he cannot keep the right foot warm, and that the red color which it first exhibits when he stands becomes pale blue. The blood-flow measurement corroborates the conclusion that in the right foot the blood is stagnating in the capillaries of the engorged area.

SUMMARY

1. In cases with marked arteriosclerosis the blood-flow in the hands is smaller and the contralateral vasomotor reflexes less pronounced than normal.

2. In cases of thoracic aneurysm the flow in the hands may be normal. Where it is subnormal there is no evidence, apart from a unilateral deficiency in some cases due to the pressure of the aneurysm, that the existence of the aneurysm as such has any influence in diminishing the flow, the diminished flow being associated with coexisting pathological conditions (myocardial changes, valvular lesions).

3. A great difference in the form of the pulse-wave in the two radials associated with thoracic aneurysm does not necessarily indicate a difference in the flow through the hands. The hand flows may be identical when the sphygmograms from the radials on the two sides are very different.

4. In three cases of Raynaud's disease the hand flows were subnormal even in the absence of an actual attack, in the more advanced cases very much below the normal.

5. An abnormally great contralateral reflex vasoconstriction to cold seems to characterize the earlier stages of Raynaud's malady. When it has existed for a long time and gangrene has occurred, the vasomotor reactions indicate the existence of anatomical changes in the vessels, which do not permit vasomotor reflexes as intense as at first.

TABLE 15. Summary of

Case	Age	Date	Pulse Rate	Blood Pressure	Temperature (C.) of				Volume of Part in c.c	
					Room	Art Blood	Calorimeters		Right	Left
							Right	Left		
Chas. S....	69	7/ 8/13	80	180, (120)	28.3	36.3	30.70	30.75	437	410
					28.3	....	30.96	.....	.....	.....
					28.3	....	31.12	.....	.....	.....
Fred S.....	58	5/ 8/13	116	122, (101)* 63	23.8	36.9	31.28	31.25	497	484
					23.9	....	31.47	.....	.....	.....
					23.9	....	31.70	.....	.....	.....
					23.9	....	31.91	.....	.....	.....
					24.0	....	31.99	.....	.....	.....
					24.2	....	32.19	.....	.....	.....
Paul K...	57	4/24/12	100	115	22.8	37.5	31.14	31.27	454	451
					22.6	....	31.52	31.54	.....	.....
Joseph C..	50	1/31/11	88	160	21.5	37.2	29.49	29.43	505	480
Wm. B.....	53	12/22/10	84	205	20.8	37.1	28.81	28.97	410	390
		1/17/11	88	210	22.2	36.9	31.07	30.82	435	410
Richard B.	38	5/23/11	100	....	27.9	37.1	31.03	30.75	495	437
					28.0	....	.....	31.09	.....	.....
					28.0	....	.....	31.26	.....	.....
					28.1	....	.....	31.41	.....	.....
					28.2	....	.....	31.66	.....	.....
Sam S....	31	12/10/12	124	L.,118,(58) R.,157,(61)	22 2	37.9	31.98	32.01	580	603
John McL..	50	8/27/12	....	156, 83	22.2	36.15	30.73	30.72	498	475
					21.2	....	30.53	30.44	1,697	1,712
		8/28/12	97	....	21.1	36.7	30.63	30.59	507	454
					20.4	....	30.87	30.76	1,780	1,749
Mrs. W. G.	28	4/24/11	108	....	25.3	37.55	30.22	30 24	391	375
					25.1	....	30.51	.....	.....	.....
					25.0	....	30.73	.....	.....	.....
					....	....	30.77	.....	.....	.....
					2.66	....	30.87	.....	.....	.....
Mrs. C. B..	29	5/ 9/13	112	....	21.7	37.35	31.09	31.10	273	282
					22.3	....	31.10	31.27	.....	.....
					22.3	....	31.11	31.21	.....	.....
					22.8	....	31.14	.....	.....	.....
					22.9	....	31.19	.....	.....	.....
					22.8	....	31.24	.....	.....	.....
					22.7	....	31.25	.....	.....	.....
					22.7	....	31.30	.....	.....	.....
Maurice T.	41	4/17/11	92	....	25.7	36.5	29.84	29.76	470	466
					26.3	....	.....	30.11	.....	.....
					26.6	....	.....	30.22	.....	.....
					25.0	....	.....	30.34	.....	.....
					25.2	....	.....	30.59	.....	.....
Anthony P.	36	10/11/12	120	....	27.8	39.15	31.90	31.92	406	460
James P...	63	4/10/12	....	....	22.0	37.05	30.51	30.59	438	414
					22.0	....	.....	30.78	.....	.....
		4/11/12	68	....	25.6	37.35	30.92	30.93	1,090	1,175
K.	50	4/16/12	116	140, 100	23.8	36.7	30.55	30.65	352	310
					24.0	....	30.44	.....	.....	.....
		4/18/12	....	....	22.5	37.1	29.55	29.72	313	304
					20.3	37.0	30.13	30.26	950	985
					20.7	....	.....	30.67	.....	.....
					21.1	....	.....	30.84	.....	.....
Miss W...	25	5/ 9/11	88	....	24.1	37.6	30.13	30.05	292	298
					24.3	....	30.19	.....	.....	.....
					24.3	....	30.23	.....	.....	.....
					24.4	....	30.24	.....	.....	.....
Chas. H....	42	12/ 5/12	100	....	23.0	37.0	31.11	31.20	961	924
		12/10/12	96	108, (88) 81	22.6	36.8	31.87	31.84	367	355
					22.9	....	.....	31.87	.....	.....
					22.7	....	.....	31.92	.....	.....
					23.6	....	.....	31.93	.....	.....

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* As in the other papers, the numbers in brackets in this column give the pressure at which the sound had disappeared.

Heat Given Off in Gram-Calories			Blood-Flow in Gm. Per Min.		Flow Per 100 c.c. of Part Per Min.		Notes
Right	Left	In Mins.	Right	Left	Right	Left	
930	822	8	23.07	20.57	5.25	5.01	Arteriosclerosis.
723	.....	8	18.81	.....	4.30	.....	Left hand in water at 8.5 C.
724	.....	7	22.18	.....	5.08	.....	Left hand in water at 43 C.
1,449	1,428	10	28.64	28.08	5.76	5.80	Arteriosclerosis.
410	.....	3	27.96	.....	5.62	.....	Left hand in water at 43 C.
1,790	.....	10	38.24	.....	7.69	.....	Left hand still in water at 43 C.
244	.....	3	18.18	.....	3.65	.....	Left hand in water at 8c.
731	.....	6	27.57	.....	5.54	.....	Left hand still in water at 8 c.
1,362	.....	10	32.13	.....	6.46	.....	Left hand in water at 38.5 C.
795	656	7	19.84	16.71	4.37	3.70	Aneurysm first seven minutes.
2,801	2,143	15	34.69	26.63	7.64	5.90	Last fifteen minutes in calorimeters.
2,580	2,460	11	33.81	31.09	6.69	6.66	Aortic aneurysm.
3,581	2,927	14	34.36	28.59	8.38	7.33	Thoracic aneurysm.
3.269	2,974	14	44.50	38.82	10.23	9.47	
3,247	2,239	11	54.03	35.62	10.91	8.15	Innominate aneurysm.
....	517	4	.....	23.89	.....	5.47	Right hand in water at 8.1 C.
....	792	4	.....	37.63	.....	8.61	Right hand still in water at 8.1 C.
....	413	3	.....	26.91	.....	6.16	Right hand in water at 4.3 C.
....	1,516	7	.....	44.23	.....	10.12	
4,466	4,292	13	64.47	62.28	11.11	10.32	Aortic aneurysm.
157	208	14	2.07	2.73	0.41	0.57	Cardio-renal disease with aneurysm.
114	100	8	2.81	2.43	0.17	0.14	Feet.
525	501	17	5.65	5.36	1.11	1.18	
616	608	10	11.74	11.37	0.66	0.65	Feet.
842	754	9	14.18	12.93	3.62	3.44	Raynaud's disease.
1,534	.....	12	20.18	.....	5.16	.....	Left hand in water at 43 C.
170	.....	3	9.23	.....	2.46	.....	Left hand in water at 12 C.
375	.....	4	15.36	.....	3.93	.....	Left hand still in water at 12 C.
477	.....	4	19.83	.....	5.07	.....	Left hand dried and wrapped.
298	299	8	6.61	6.64	2.42	2.35	Raynaud's disease first eight minutes.
795	1,079	16	8.83	12.12	3.23	4.29	Next sixteen minutes in calorimeters.
392	415	7	9.97	10.73	3.65	3.80	Last seven minutes of the sixteen.
200	.....	2	17.89	.....	6.55	.....	Left hand in water at 43 C.
651	.....	10	11.74	.....	4.30	.....	Left hand still in water at 43 C.
167	.....	2	15.18	.....	5.56	.....	Left hand in water at 12 C.
118	.....	2	10.74	.....	3.93	.....	Left hand still in water at 12 C.
477	.....	5	1,752	.....	6.41	.....	Left hand still in water at 12 C.
1.491	1.111	8	31.09	22.89	6.67	4.87	Arteritis in leg.
....	347	5	.....	12.07	.....	2.59	Right hand in water at 9 C.
....	589	4	.....	26.06	.....	5.59	Right hand still in water at 9 C.
....	382	3	.....	22.97	.....	4.93	Right hand in water at 43 C.
....	1,630	6	.....	51.09	.....	10.96	Right hand still in water at 43 C.
324	336	10	4.96	5.16	1.22	1.12	Gangrene of fingers; septic endocarditis.
1,033	1,199	15	11.59	13.75	2.65	3.32	Diabetes.
....	1,027	11	.....	16.54	.....	3.99	Right hand in water at 43 C.
2,023	2,858	23	15.19	21.50	1.39	1.83	Feet (left gangrenous).
95	87	18	0.95	0.88	0.27	0.28	Myocarditis; cyanosis. (Congenital heart?)
44	.....	10	0.78	.....	0.22	.....	Left hand in water at 41.8 C.
335	434	15	3.29	4.35	1.05	1.43	Cyanosis much less.
2,912	4.712	23	20.47	33.77	2.15	3.42	Feet (left toes gangrenous).
....	1.357	9	.....	26.46	.....	2.68	Right foot in water at 10.5 C.
....	1,726	11	.....	28.30	.....	2.87	Right foot in water at 42 C.
467	300	R 11 L 9	6.32	4.90	2.16	1.64	Purpura.
372	.....	8	6.97	.....	2.38	.....	Left hand in water at 43 C.
234	.....	7	5.04	.....	1.72	.....	Left hand in water at 9.1 C.
133	.....	4	5.04	.....	1.72	.....	Left hand dried and wrapped.
474	1,192	18	4.96	12.67	0.51	1.37	Feet (edema of right).
559	588	10	12.59	13.17	3.43	3.71	Hands.
....	210	4	.....	11.83	.....	3.33	Right hand in water at 42.8 C.
....	700	11	.....	14.49	.....	4.08	Right hand still in water at 42.8 C.
....	321	10	.....	7.32	.....	2.06	Right hand in water at 8.6 C.

the abrupt change in the sound occurred; the smaller number following is the pressure at which

CHRONIC GASTRIC ULCER AND ITS RELATION TO GASTRIC CARCINOMA*

REVIEW OF SIX HUNDRED EIGHTY-FOUR SPECIMENS †

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AND
ALBERT COMPTON BRODERS, M.D.
MAYO CLINIC
ROCHESTER, MINN.

The discussion which is going on in the literature over the question of whether or not gastric carcinoma develops on chronic gastric ulcer and regarding the percentage of chronic ulcers which "become" carcinomatous, is, it seems to us, a discussion which is not only dealing with an unanswerable question with our present methods of investigation, but is also doing a great deal of unnecessary harm to mankind by preventing rational treatment. Viewed from the standpoint of feasibility of scientific investigation, such discussion seems superfluous for the following reasons: 1. No one has seen a chronic gastric ulcer in the process of development. 2. No one has been able to witness the stages of reaction to irritation through which the tissues of the gastric wall pass during the formation of ulcer or carcinoma. 3. No one has ever recognized carcinoma in the process of development anywhere in man or other animal. 4. Even the most skilful cellular pathologist cannot point out the line of demarcation between simple hyperplastic cells of the mucosa of a simple chronic ulcer and malignant hyperplastic cells of a chronic ulcer which is associated with carcinoma. 5. No one has experimentally produced a carcinoma.

With these fundamental limitations of our knowledge, one can only view the conditions as they occur. The known facts which are seen in the specimens herewith presented are the following:

1. Single and multiple chronic ulcerations occur in the stomach (Figs. 1, 2, 13 and 18).

2. They vary widely in size (diameter and depth), as in Figures 1, 2, 5, 6, 8, 9, 10, 11, 13. 14, 18, 19, 29 and 33.

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* Read before the Southern Minnesota Medical Society, Mankato, Aug. 5, 1913, and before the Kentucky Medical Society, Sept. 2, 1913.

† This number includes 218 specimens previously reported by MacCarty at the meeting of the American Medical Association, June, 1909, and published in Surgery, Gynecology and Obstetrics, May, 1910.

3. The characteristics of simple chronic gastric ulcers consist of excavations in the wall of the stomach, and these excavations may have the mucosa, muscularis mucosae, submucosa, musculature, subserosa or perigastric structures for their bases, depending on their depth (Figs. 2, 3, 4, 6, 9, 11, 14, 19, 20, 29, 30, 34, 35, 37 and 38).

4. The excavations may be wide and shallow (Fig. 2) or narrow and deep (Figs. 8, 9, 37 and 38).

5. The mucosa of the borders of gastric ulcers may gradually recede from the base or overhang the base (Figs. 2, 14 and 34).

6. The epithelium of the mucosa, which is the most natural source of carcinoma, may be normal (differentiated), as in Figures 15, 16 and 24; hyperplastic (partially differentiated), as in Figures 23 and 25, or irregularly hyperplastic and migratory (extra glandular or in the stroma), as in Figures 31, 32 and 36.

7. The bases of chronic gastric ulcers consist of scar tissue which radiates usually from the center of the ulcer or is perpendicular to the plane of the coats of the stomach (Figs. 7, 12, 20, 30, and 35).

8. Usually the surface of the base is composed of necrotic tissue which is infiltrated with lymphocytes (Figs. 7, 12, 17, 20, 21, 30 and 35).

9. Carcinomatous cells occur in the lower parts of the mucosa and in the immediate submucosa without their being present in the base (Figs. 30, 31 and 32).

10. Of 684 specimens which were either excised or resected from the stomach, 191 were chronic ulcers or ulcers in which no histologic evidence of carcinoma was present. There were 472 specimens which presented the characteristics of simple ulcer plus the presence of carcinoma and twenty-one specimens of ulcer in which the presence of cancer was doubtful. The ulcer which contains the smallest amounts of carcinomatous cells contains these in the mucosa of the borders and not in the base. The earliest carcinomatous condition of the cells is not seen in so-called "cut-off" epithelium, in scar tissue of the base, but is seen in the epithelium of the mucosa (Figs. 26, 27, 31 and 32).

Without regard to clinical history, certain conclusions may be drawn from the facts enumerated above:

1. Single and multiple chronic ulcers occur in the stomach.

2. Single and multiple chronic gastric ulcers occur with all the characteristics of simple ulcers plus the presence of carcinomatous cells in their borders minus the presence of similar cells in the bases.

3. Simple and multiple gastric ulcers occur which present the macroscopic characteristics of simple ulcer plus the presence of carci-

noma in the borders and bases, indeed, with glandular involvement and metastases.

The question for the clinician and the surgeon is not "Does gastric carcinoma develop on gastric ulcers and what percentage of ulcers become malignant?" but "Has the proved association of gastric carcinoma with chronic gastric ulcer sufficient significance to be of prognostic value in cases clinically diagnosticated as gastric ulcer?"

The association of these two conditions in conjunction with the fact that the immediate operative mortality, the postoperative mortality and the subsequent duration of life after gastric resection bear a definite relation to the extent of the carcinomatous involvement[1] should be sufficient to stimulate a consideration on the part of every physician of the possibility of chronic gastric ulcers not only becoming but actually being carcinomatous.

The question of differential diagnosis in such cases may also be answered by facts, the most salient of which is the fact that the differential diagnosis is often to be made only by a cellular pathologist after the removal of the tissue and not by the clinician or surgeon.

Do we know of any method other than exploration and microscopic examination which positively answers the question of whether or not a specimen inside or outside the body is carcinoma? The clinical history, gastric analysis, roentgenoscopy and serum diagnosis cannot positively differentiate these groups of cases, especially those without pyloric obstruction. Indeed, the microscope, which is our present highest court of appeal, can do no more than to divide the specimens into three groups, namely, simple ulcer group, carcinoma group and a doubtful group. Whenever the clinician feels positive of the clinical diagnosis of chronic gastric ulcer he should consider that carcinoma can not be ruled by our present methods of clinical investigation.

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[1] MacCarty and Blackford: Involvement of Regional Lymphatic Glands in Carcinoma of the Stomach, Ann. Surg., June, 1912.

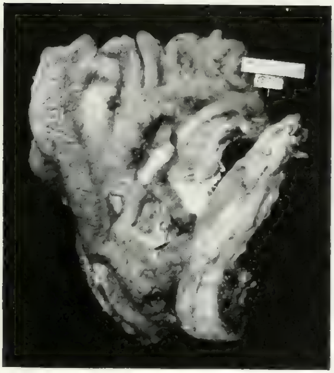

Fig. 1 (18088).—Multiple chronic gastric ulcers in various degrees of extension.

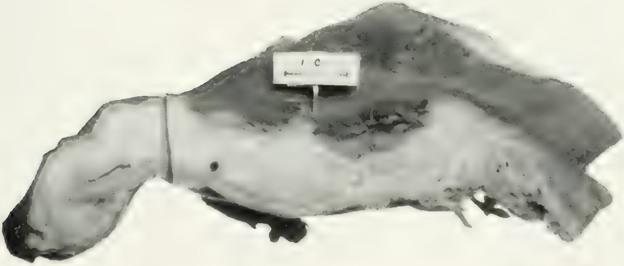

Fig. 2 (18088).—Gross section through four ulcers showing the degrees of extension through the wall of the stomach.

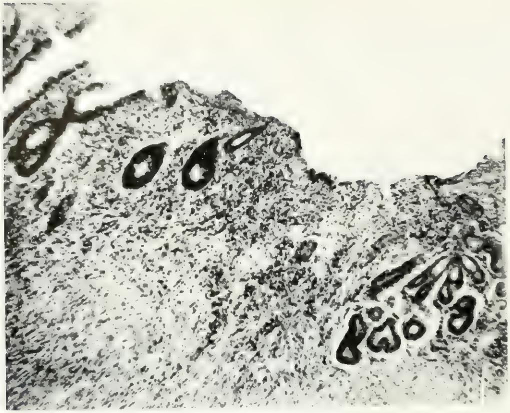

Fig. 3 (18088).—Low-power photograph through the smallest ulceration in Figures 1 and 2. The destruction has not extended through the muscularis mucosae. Some distortion of the glands and lymphocytic infiltration of the mucosa.

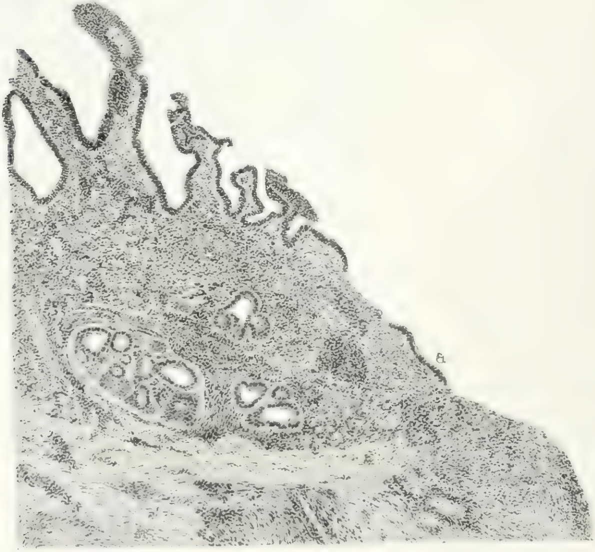

Fig. 4 (18088).—Low-power drawing through the wall and part of the base of the ulcer second in size in Figures 1 and 2. The destruction has extended through the muscularis mucosae and into the submucosa. There is extensive distortion of the glands and also lymphocytic infiltration.

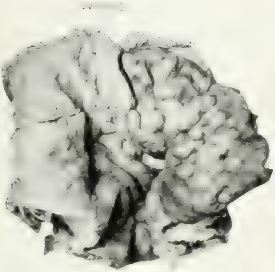

Fig. 5.

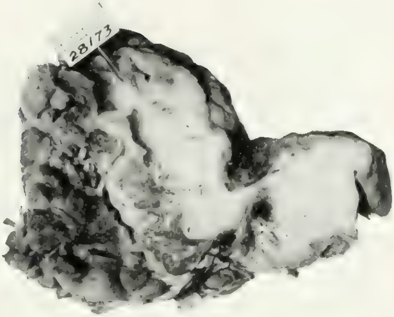

Fig. 6.

Fig. 5 (28173).—Single simple chronic gastric ulcer.

Fig. 6 (28173).—Gross section through the ulcer in Figure 5 showing the depth and extensive scar tissue of the base. The ulceration has extended through all of the gastric coats.

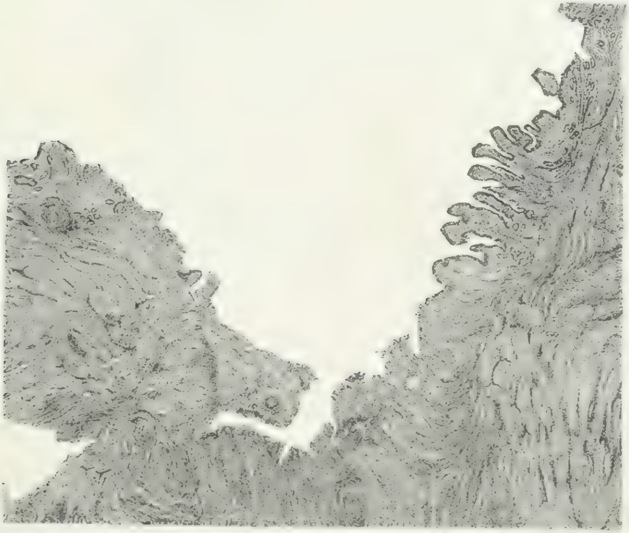

Fig. 7 (28173).—Low-power drawing through the specimen in Figures 5 and 6 showing the characteristics of a simple chronic gastric ulcer. Destruction, distortion of the mucosa, lymphocytic infiltration, necrosis of the tissue in the base, and the peculiar arrangement of the scar tissue in the base.

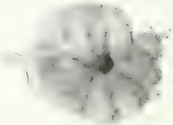

Fig. 8.

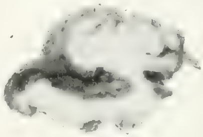

Fig. 9.

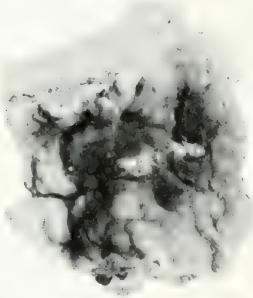

Fig. 10.

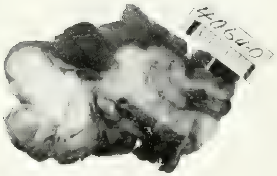

Fig. 11.

Figs. 8, 9, 10 and 11 (37378 and 40640).—Photographs showing simple chronic gastric ulcers.

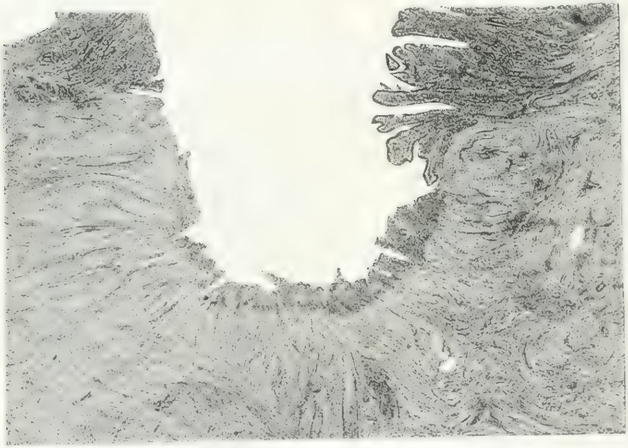

Fig. 12 (27381).—Low-power drawing showing the characteristics of a simple chronic gastric ulcer.

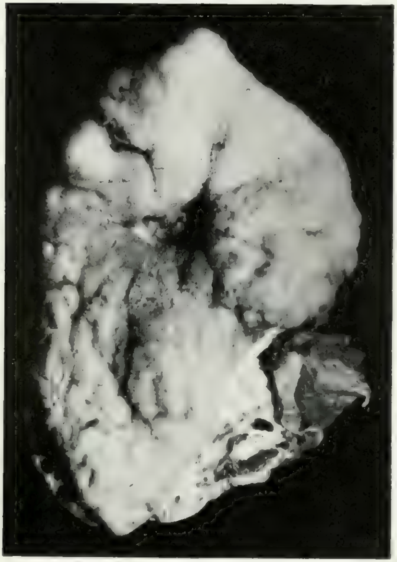

Fig. 13.

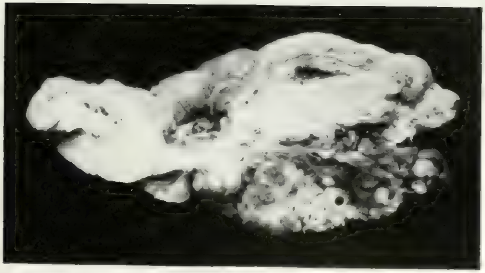

Fig. 14.

Figs. 13 and 14 (49687).—Photographs of a simple chronic gastric ulcer.

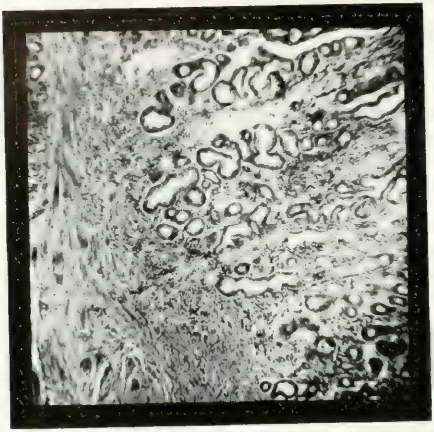

Fig. 15.

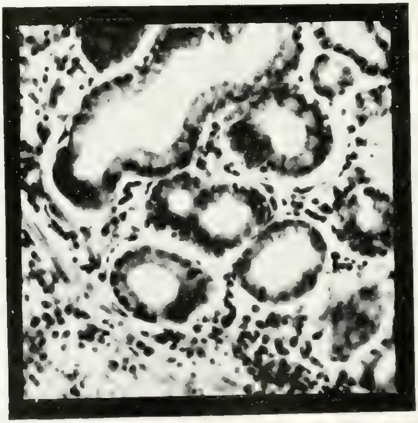

Fig. 16.

Figs. 15 and 16 (48401).—Low-power photographs showing the character of the glands of the mucosa in a simple chronic gastric ulcer. The epithelium consists of definitely differentiated cells which still retain the characteristics of the normal gastric epithelium.

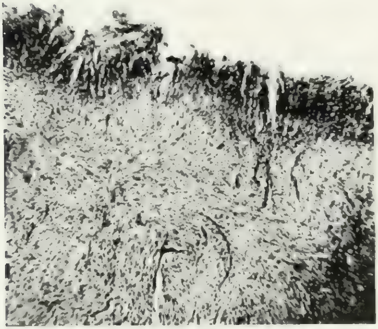

Fig. 17 (48401).—Low-power photograph through the base of a simple chronic gastric ulcer showing lymphocytic infiltration and scar tissue.

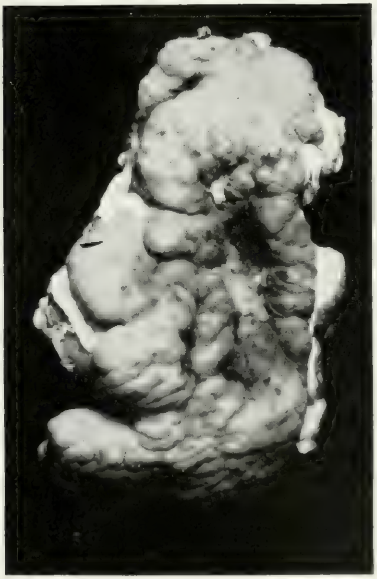

Fig. 18.

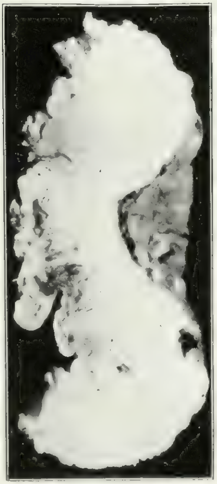

Fig. 19.

Figs. 18 and 19 (A53435).—Photographs of a simple chronic gastric ulcer.

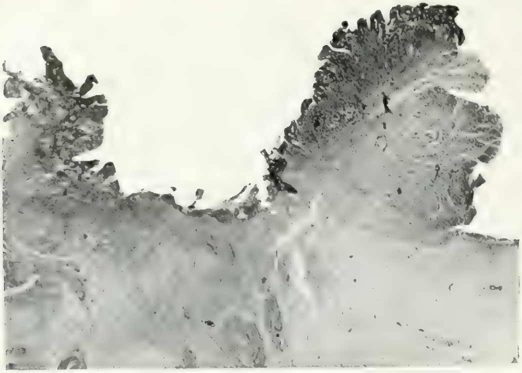

Fig. 20 (53630).—Low-power photograph through a simple chronic gastric ulcer.

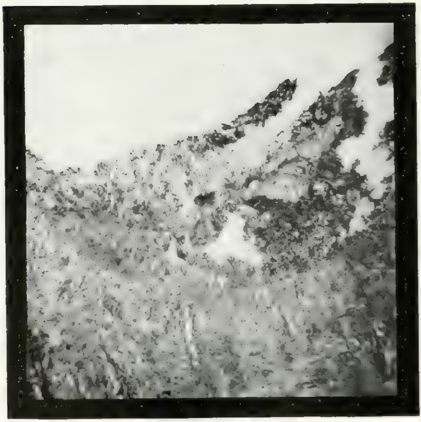

Fig. 21 (53630).—Low-power photograph through the base of the ulcer in Figure 21.

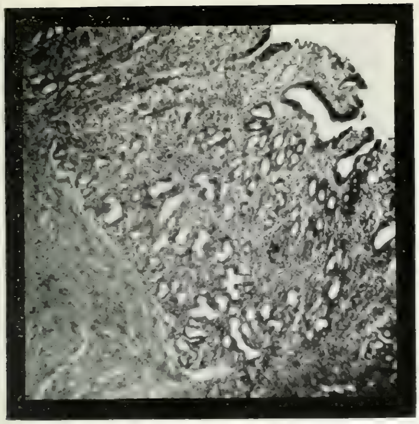

Fig. 22.

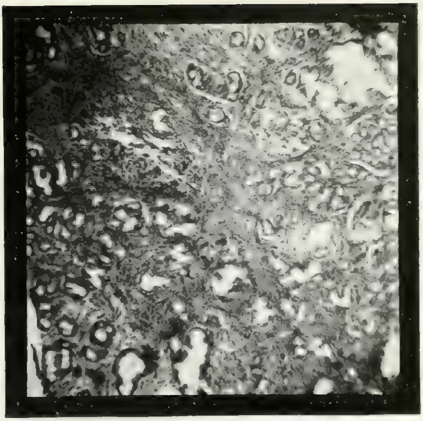

Fig. 23.

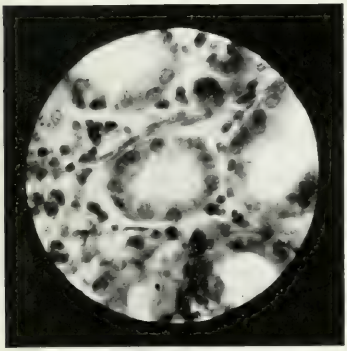

Fig. 24.

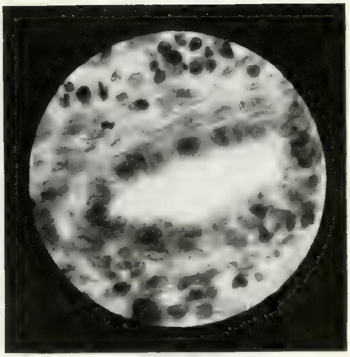

Fig. 25.

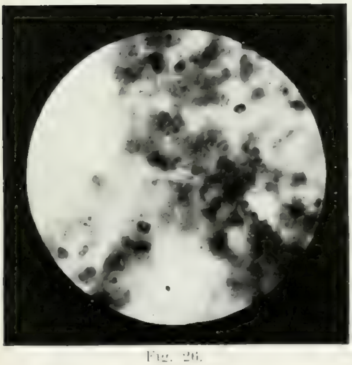

Fig. 26.

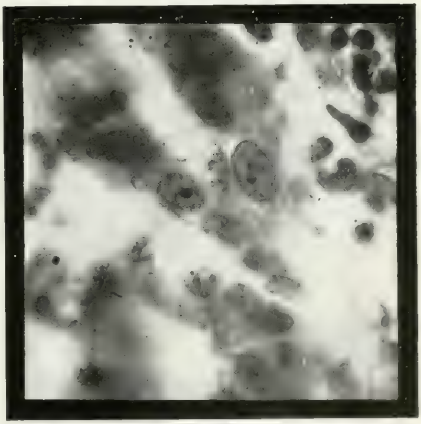

Fig. 27.

Figs. 22, 23, 24, 25, 26 and 27 (53630).—Photograph of the epithelium in the mucosa of the borders of a chronic gastric ulcer (Fig. 20). The glands are more irregular than those seen in Figures 15 and 16. The cells are not so typically differentiated as those in Figure 16, and still there is no definite invasion of the stroma. The cells resemble many of those which are seen in carcinoma (Figs. 31, 32 and 36).

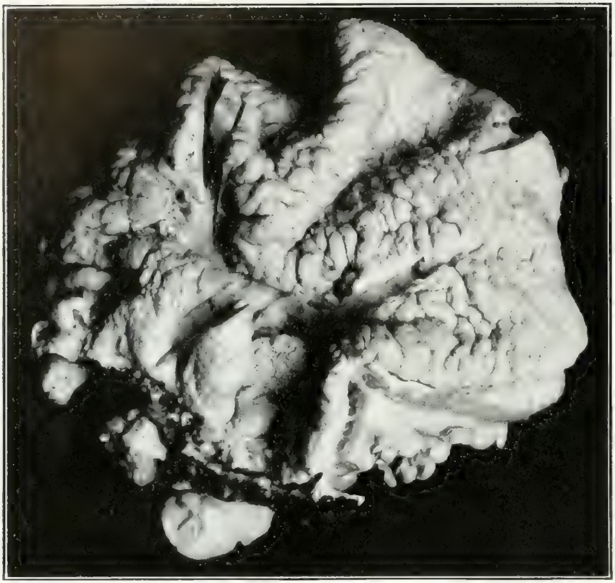

Fig. 28.

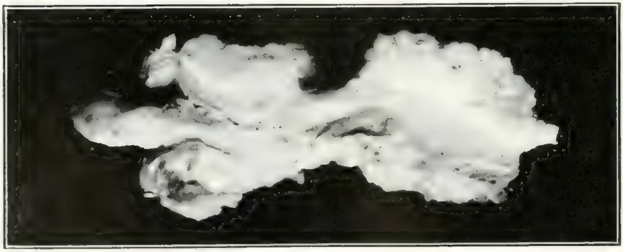

Fig. 29.

Figs. 28 and 29 (35572).—Photographs through a chronic gastric ulcer.

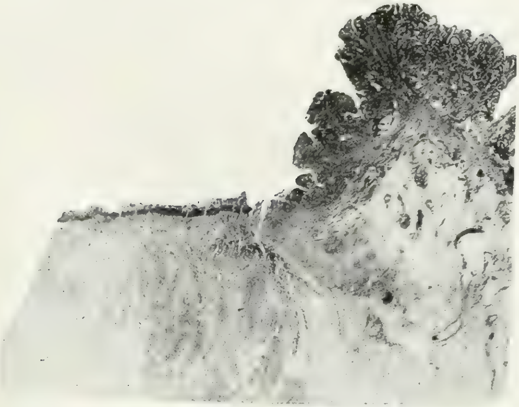

Fig. 30 (35572).—Low-power photograph through the ulcer which is seen in Figures 28 and 29. The characteristics of simple chronic gastric ulcer may be seen to exist. There is no apparent carcinoma in the base.

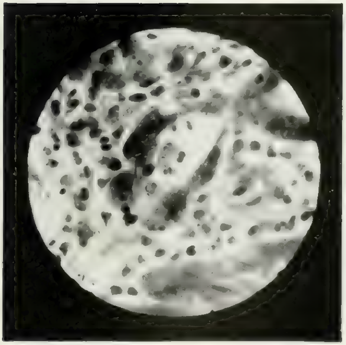

Fig. 31.

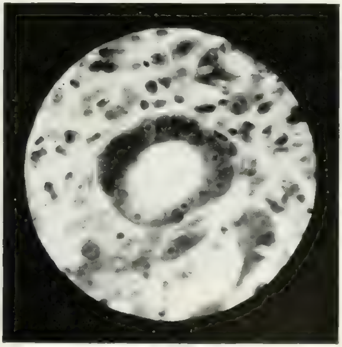

Fig. 32.

Figs. 31 and 32 (35572).—Photographs of undifferentiated, irregular epithelial cells in the submucosa just below the muscularis mucosae. The cells are typical of carcinoma.

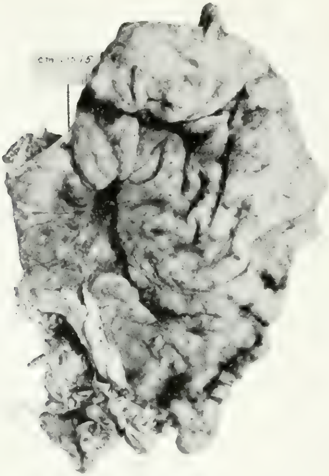

Fig. 33.

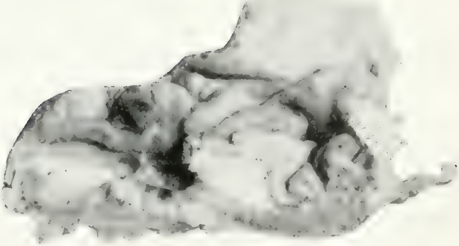

Fig. 34.

Figs. 33 and 34 (21555).—Photographs of chronic gastric ulcers.

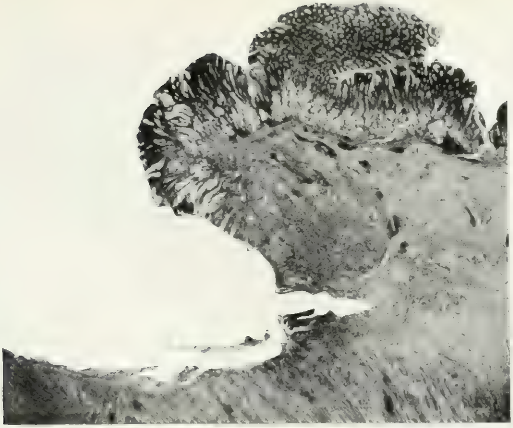

Fig. 35 (21555).—Low-power drawing through the border and part of the base of the ulcer, showing the presence of carcinoma in the mucosa and just below the mucosa, but none in the base. Direct connection between the glands of the mucosa and the carcinoma may be seen.

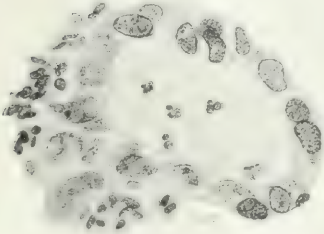

Fig. 36.

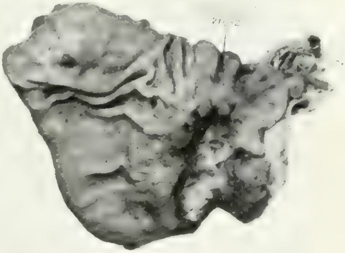

Fig. 37.

Fig. 36 (21555).—High-power drawing through an epithelial carcinomatous island in the submucosa of the gastric ulcer in Figs. 33 and 34.

Fig. 37 (21882).—Chronic gastric ulcer plus the presence of carcinoma.

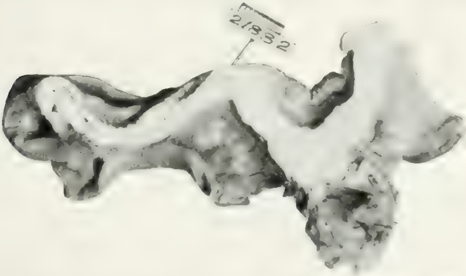

Fig. 38 (21882).—Gross section through the carcinomatous ulcer which is seen in Figure 37.

THE NON-PROTEIN NITROGENOUS CONSTITUENTS OF THE BLOOD IN CHRONIC VASCULAR NEPHRITIS (ARTERIOSCLEROSIS) AS INFLUENCED BY THE LEVEL OF PROTEIN METABOLISM *

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By virtue of the analytical technic recently introduced by Folin and Denis for the analysis of blood it has become possible to study the retention of nitrogenous waste products with far greater ease and certainty than formerly. Such studies are particularly to be desired in the investigation of nephritis, for urine analyses cannot reveal the stage of accumulation of such products, an accumulation which may vary between almost normal figures and those accompanying uremia. According to Strauss, the high blood-pressure of nephritis is usually or at least frequently accompanied by an excessive accumulation of the nitrogenous waste products, whereas edema is rather associated with a retention of chlorids. For the investigation reported in this paper we have selected a group of patients whose blood-pressure varied between 160 and 225 mm.

The chief purpose of our investigation was to determine the extent to which it is possible by means of diets to vary, particularly to reduce, the waste nitrogen in the blood of such nephritis and incidentally determine whether there is any relationship between the blood-pressure and the accumulations of nitrogenous waste products in the blood. With regard to the latter point, the details of our results will be described by one of us (Seymour) in a separate paper, though a few figures for the blood-pressure are recorded in Tables 1 to 12. We have included in the work a series of "kidney efficiency" tests, according to the phenolsulphonephthalein method recently introduced by Rowntree and Geraghty, in order to obtain further comparisons between the values given by that test and the actual accumulation as revealed by blood analyses. While hospital records were kept of the diet of each patient, we omit all such data and give the urinary nitrogen alone as the index of the total protein metabolism. The subjects of these experiments were inmates of an institution maintained on Long Island, Boston Harbor, by the city of Boston for the accommodation of indigent individuals. They were

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* From the Laboratories of Biologic Chemistry and Theory and Practice of Harvard Medical School and the Long Island Hospital.

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selected mainly on the basis of abnormally high blood-pressures, and were removed from the institute and placed in a special ward in the Long Island Hospital.

With the exception of Charles M., all of these patients were allowed to be out of bed during the day; but in order to control the collection of urine and the diets, they were not permitted to leave their own ward, except to go on an adjoining veranda. The patients were under the constant supervision of a special nurse and orderly, who were placed at our disposal for this purpose by the hospital authorities.

It was originally our intention to divide the time covered by the experiment into three periods: (1) a period in which the patients would be allowed to eat at will the ordinary ward diet; (2) a period of high protein feeding; (3) a period of low protein diet with high calorific intake. The diets proposed for the first and third periods were successfully administered, but during the period of high protein feeding we were, as will be seen on examination of the figures for urinary nitrogen, unable to raise the protein metabolism to a very high level. This failure was due to the nausea and vomiting which occurred in many cases during that part of the experiments.

During the second or "high protein" period beside the administration of a liberal supply of meat and eggs at the three regular meals, two to three egg-nogs daily were given between meals.

During the third or low protein period the diet consisted of apple-tapioca pudding, boiled or fried rice, boiled potatoes with butter, fruit (oranges, apples and stewed pears) and boiled cabbage. In addition, during this period, each patient took daily 150 to 200 gm. of arrowroot starch, which had been rendered soluble with diastase. This soluble starch was served hot, flavored with fruit juice or with a little port wine or whisky.

During the entire experiment smoking was allowed, and coffee was served three times daily.

The crucial point which we set out to determine, namely, whether by low nitrogen diets it is possible to reduce the urea and total non-protein nitrogen of blood to the normal or less is abundantly proven by the tabular records of the preceding twelve nephritic patients. In every case the figures for the retention nitrogen obtained at the end of the third period, the low protein period, are down substantially to the figures obtained from strictly normal persons (from 22 to 28 mg. non-protein nitrogen and from 11 to 14 mg. urea nitrogen).

The original level of retention was, to be sure, not very high in several of these patients. The patients had been selected chiefly on the basis of the blood-pressure, and high blood-pressure is not necessarily accompanied by excessive retention of nitrogenous waste products. Judging

TABLE 1.—Result of Test in Case 1.

Daniel B., aged 60, weight 63.5 kg. Diagnosis: Aortic roughening and regurgitation, chronic interstitial nephritis.

Diet	Date	Urine		Blood (100 gm.)			Phenolsulphonephthalein Excretion in 2 Hrs. Per Cent.	Blood-Pressure
		Vol. c.c.	Nitrogen gm.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	960	9.7	..	..	...	26	175
Ward	4/11/13	1,080	9.9					
Ward	4/12/13	930	9.7					
Ward	4/13/13	1,020	9.2					
Ward	4/14/13	1,050	8.4	40	18	1.9	22	145
High protein	4/16/13	1,020	8.9	..	..	...	..	160
High protein	4/17/13	1,080	10.3					
High protein	4/18/13	1,140	12.6	..	..	...	38	
High protein	4/20/13	1,560	11.2					
High protein	4/21/13	1,020	9.7	40	20	2.7	26	155
Low protein	4/23/13	1,020	7.9	..	..	...	..	140
Low protein	4/24/13	1,050	11.5					
Low protein	4/25/13	1,080	5.5					
Low protein	4/26/13	1,080	3.5					
Low protein	4/27/13	1,200	2.7	21	11	2.5	45	170
Average	....	.....	....	..	..	...	31.6	

TABLE 2.—Result of Test in Case 2

Thos. H. M., aged 57, weight 80.5 kg. Diagnosis: Chronic interstitial nephritis, hypertrophy of heart, arteriosclerosis.

Diet	Date	Urine		Blood (100 gm.)			Phenolsulphonephthalein Excretion in 2 Hrs. Per Cent.	Blood-Pressure
		Vol. c.c.	Nitrogen gm.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	960	8.4	..	..	...	..	180
Ward	4/11/13	450	5.1					
Ward	4/12/13	780	7.4					
Ward	4/13/13	1,080	8.4					
Ward	4/14/13	1,140	8.0	44	26	1.7	12	190
High protein	4/16/13	900	7.5	..	..	...	..	185
High protein	4/17/13	1,020	8.1					
High protein	4/18/13	1,140	8.4	..	..	...	22	
High protein	4/20/13	1,620	12.4					
High protein	4/21/13	1,560	15.0	44	24	2.7	36	160
Low protein	4/23/13	1,440	9.8	..	..	...	..	190
Low protein	4/24/13	900	6.6					
Low protein	4/25/13	1,500	6.0					
Low protein	4/26/13	1,200	4.4					
Low protein	4/27/13	1,630	4.2	19	10	1.7	35	208
Average	....	.....	....	..	..	...	26.2	

TABLE 3.—Result of Test in Case 3

William McG., aged 71, weight 67.5 kg. Diagnosis: Arteriosclerosis, chronic emphysema, chronic interstitial nephritis.

Diet	Date	Urine		Blood (100 gm.)			Phenol-sulphone-phthalein Excretion in 2 Hrs. Per Cent.	Blood-Pressure
		Vol. c.c.	Nitrogen gm.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	900	7.0	..	..	...	..	160
Ward	4/11/13	510	5.1					
Ward	4/12/13	900	9.0					
Ward	4/13/13	1,020	7.5					
Ward	4/14/13	1,350	7.8	38	20	2.2	34	160
High protein	4/16/13	1,020	9.2	..	..	...	..	160
High protein	4/17/13	905	8.2					
High protein	4/18/13	1,020	10.8	..	..	...	29	
High protein	4/20/13	1,380	11.3					
High protein	4/21/13	1,080	10.6	37	20	2.3	34	160
Low protein	4/23/13	1,920	7.4	..	..	...	..	145
Low protein	4/24/13	900	9.0					
Low protein	4/25/13	1,440	5.3					
Low protein	4/26/13	1,500	7.1					
Low protein	4/27/13	1,260	3.3	23	11	2.0	37	158
Average	....	.....	....	..	..	...	33.5	

TABLE 4.—Result of Test in Case 4

Timothy, W. C., aged 71, weight 91.5 kg. Diagnosis: Right inguinal hernia, arteriosclerosis, senility, chronic interstitial nephritis.

Diet	Date	Urine		Blood (100 gm.)			Phenol-sulphone-phthalein Excretion in 2 Hrs. Per Cent.	Blood-Pressure
		Vol. c.c.	Nitrogen gm.	Non-Nitrogen Protein mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	.....	....	..	..	...	..	175
Ward	4/11/13	570	5.4					
Ward	4/12/13	1,560	11.2					
Ward	4/13/13	1,230	8.8					
Ward	4/14/13	2,070	12.0	49	25	2.6	..	170
High protein	4/16/13	1,560	10.1	..	..	...	..	142
High protein	4/17/13	1,440	13.7					
High protein	4/18/13	1,560	14.8	..	..	...	31	
High protein	4/20/13	1,080	16.2					
High protein	4/21/13	1,440	18.7	48	23	2.6	39	165
Low protein	4/23/13	1,080	8.7	..	..	...	..	140
Low protein	4/24/13	1,050	10.4					
Low protein	4/25/13	1,620	6.5					
Low protein	4/26/13	1,980	5.9					
Low protein	4/27/13	2,040	5.2	22	10	1.8	50	158
Average	....	.....	....	..	..	...	46.6	

TABLE 5.—Result of Test in Case 5

Nathan, D. L., aged 81, weight 78.5 kg. Diagnosis: Arteriosclerosis, senility, cardiac hypertrophy, chronic interstitial nephritis.

Diet	Date	Urine		Blood (100 gm.)			Phenolsulphonephthalein Excretion in 2 Hrs. Per Cent.	Blood-Pressure
		Vol. c.c.	Nitrogen gm.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	1,290	7.8	..	..	...	..	210
Ward	4/11/13	600	5.7					
Ward	4/12/13	1,110	7.8					
Ward	4/13/13	1,140	8.5					
Ward	4/14/13	1,590	12.2	50	28	2.7	14	198
High protein	4/16/13	1,260	8.4	..	..	...	..	188
High protein	4/17/13	990	8.5					
High protein	4/18/13	1,200	12.0	..	..	...	20	
High protein	4/20/13	1,440	11.0					
High protein	4/21/13	1,050	10.0	58	40	3.3	17	235
Low protein	4/23/13	1,440	6.7	..	..	...	..	170
Low protein	4/24/13	1,080	6.9					
Low protein	4/25/13	960	4.5					
Low protein	4/26/13	1,500	5.7					
Low protein	4/27/13	1,920	4.3	23	12	2.0	28	203
Average	....	.....	....	..	..	...	19.8	

TABLE 6.—Result of Test in Case 6

Martin, T. D., aged 54, weight 71.5 kg. Diagnosis: Arteriosclerosis, chronic interstitial nephritis.

Diet	Date	Urine		Blood (100 gm.)			Phenolsulphonephthalein Excretion in 2 Hrs. Per Cent.	Pressure Blood-
		Vol. c.c.	Nitrogen gm.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	1,260	11.1	..	..	...	35	235
Ward	4/11/13	1,050	10.5					
Ward	4/12/13	930	6.4					
Ward	4/13/13	1,530	7.8					
Ward	4/14/13	1,710	8.7	39	18	3.0	33	187
High protein	4/16/13	1,020	8.3	..	..	...	..	200
High protein	4/17/13	1,500	13.1					
High protein	4/18/13	1,260	9.6	..	..	...	23	
High protein	4/20/13	2,040	14.1					
High protein	4/21/13	1,620	13.6	62	45	3.9	30	180
Low protein	4/23/13	1,320	8.5	..	..	...	..	160
Low protein	4/24/13	1,200	7.7					
Low protein	4/25/13	1,500	6.1					
Low protein	4/26/13	1,560	5.6					
Low protein	4/27/13	1,560	4.8	30	15	2.7	29	190
Average	....	.....	....	..	..	...	30	

TABLE 7.—Result of Test in Case 7

Edward R., aged 74, weight 59.5 kg. Diagnosis: Inguinal hernia, arteriosclerosis, chronic interstitial nephritis.

Diet	Date	Urine		Blood (100 gm.)			Phenol-sulphone-phthalein Excretion in 2 Hrs. Per Cent.	Blood-Pressure
		Vol. c.c.	Nitrogen gm.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	1,260	7.4	..	..	...	..	225
Ward	4/11/13	840	6.8					
Ward	4/12/13	1,410	9.4					
Ward	4/13/13	1,350	10.3					
Ward	4/14/13	1,250	9.8	50	28	2.2	21	190
High protein	4/16/13	1,380	9.1	..	..	...	..	200
High protein	4/17/13	1,140	9.5					
High protein	4/18/13	1,860	11.5	..	..	...	29	
High protein	4/20/13	1,920	11.7					
High protein	4/21/13	1,380	11.1	82	67	3.9	26	180
Low protein	4/23/13	1,500	6.7	..	..	...	..	190
Low protein	4/24/13	1,440	7.5					
Low protein	4/25/13	1,560	4.9					
Low protein	4/26/13	1,080	3.3					
Low protein	4/27/13	900	1.9	26	12	2.3	35	190
Average	....	.....	....	..	..	...	28	

TABLE 8.—Result of Test in Case 8

Michael O'C., aged 66, weight 90.5 kg. Diagnosis: Arteriosclerosis, chronic emphysema, cardiac hypertrophy, chronic interstitial nephritis.

Diet	Date	Urine		Blood (100 gm.)			Phenol-sulphone-phthalein Excretion in 2 Hrs. Per Cent.	Pressure Blood-
		Vol. c.c.	Nitrogen gm.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	1.110	10.1	..	..	...	..	195
Ward	4/11/13	720	6.7					
Ward	4/12/13	1,050	11.4					
Ward	4/13/13	1.260	9.9					
Ward	4/14/13	1,170	11.1	28	14	2.5	34	198
High protein	4/16/13	1,440	11.1	..	..	...	..	240
High protein	4/17/13	1,380	11.3					
High protein	4/18/13	1,020	10.6	..	..	...	23	
High protein	4/20/13	1,446	14.4					
High protein	4/21/13	1,680	15.3	30	15	2.5	..	210
Low protein	4/23/13	1.080	10.8	..	..	...	..	180
Low protein	4/24/13	1,320	10.9					
Low protein	4/25/13	1,440	6.3					
Low protein	4/26/13	1,020	2.4					
Low protein	4/27/13	1,500	3.8	20	11	2.6	30	150
Average	....	.....	....	..	.	...	29	

TABLE 9.—Result of Test in Case 9

William T. W., aged 59, weight 70.5 kg. Diagnosis: Left hemiplegia, mitral regurgitation and aortic roughening, chronic interstitial nephritis, arteriosclerosis.

Diet	Date	Urine		Blood (100 gm.)			Phenolsulphonephthalein Excretion in 2 Hrs. Per Cent.	Blood-Pressure
		Vol. c.c.	Nitrogen gm.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	720	4.8	..	..	...	..	175
Ward	4/11/13	480	5.1					
Ward	4/12/13	1,050	5.4					
Ward	4/13/13	1,020	9.8					
Ward	4/14/13	1,110	7.4	27	14	2.6	..	170
High protein	4/16/13	1,020	7.0	..	..	...	..	172
High protein	4/17/13	1,080	9.6					
High protein	4/18/13	1.080	9.0	..	..	...	26	
High protein	4/20/13	1,560	13.0					
High protein	4/21/13	.....	....	30	16	2.8	31	140
Low protein	4/23/13	1,500	7.0	..	..	...	..	160
Low protein	4/24/13	1,050	7.8					
Low protein	4/25/13	1,200	3.5					
Low protein	4/26/13	720	2.6					
Low protein	4/27/13	1.620	3.3	20	11	2.3	24	190
Average	....	.....	....	..	..	...	27	

TABLE 10.—Result of Test in Case 10

John De W., aged 82, weight 80 kg. Diagnosis: Cardiac hypertrophy, arteriosclerosis, chronic interstitial nephritis.

Diet	Date	Urine		Blood (100 gm.)			Phenolsulphonephthalein Excretion in 2 Hrs. Per Cent.	Blood-Pressure
		Vol. c.c.	Nitrogen gm.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	750	7.3	..	..	...	23	170
Ward	4/11/13	540	5.8					
Ward	4/12/13	600	6.4					
Ward	4/13/13	1,110	9.2					
Ward	4/14/13	1,470	7.9	30	15	2.5	35	150
High protein	4/16/13	1,020	8.2	..	..	...	..	154
High protein	4/17/13	1,200	12.0					
High protein	4/18/13	960	12.5	..	..	...	16	
High protein	4/20/13	2,040	10.1					
High protein	4/21/13	1,500	19.6	30	15	3.0	18	145
Low protein	4/23/13	1,020	7.7	..	..	...	..	135
Low protein	4/24/13	1,050	9.8					
Low protein	4/25/13	1.440	5.3					
Low protein	4/26/13	1,560	4.7					
Low protein	4/27/13	1.560	3.4	19	10	...	20	140
Average	....	.....	....	..	..	...	28	

TABLE 11.—Result of Test in Case 11

Frank M., aged 72, weight 89.5 kg. Diagnosis: Arteriosclerosis, cardiac hypertrophy, chronic interstitial nephritis.

Diet	Date	Urine		Blood (100 gm.)			Phenol-sulphone-phthalein Excretion in 2 Hrs. Per Cent.	Blood-Pressure
		Vol. c.c.	Nitrogen gm.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	1,110	15.0	..	..	...	..	225
Ward	4/11/13	570	5.6					
Ward	4/12/13	1,050	8.5					
Ward	4/13/13	1,560	9.5					
Ward	4/14/13	2,040	9.6	30	15	2.6	29	190
High protein	4/16/13	1,440	11.5	..	..	...	..	220
High protein	4/17/13	1,560	12.3					
High protein	4/18/13	1,560	14.2	..	..	...	27	
High protein	4/20/13	1,560	13.0					
High protein	4/21/13	1,920	14.8	32	16	2.8	39	200
Low protein	4/23/13	1,020	7.0	..	..	...	..	180
Low protein	4/24/13	1,440	7.5					
Low protein	4/25/13	1,680	4.8					
Low protein	4/26/13	1,620	4.6					
Low protein	4/27/13	2,100	4.2	19	10	2.0	33	200
Average	....	.....	....	..	..	...	32	

TABLE 12.—Result of Test in Case 12

Chas. McL., aged 63, weight 90.5 kg. Diagnosis: Cardiac hypertrophy, arteriosclerosis, chronic interstitial nephritis.

Diet	Date	Urine		Blood (100 gm.)			Phenol-sulphone-phthalein Excretion in 2 Hrs. Per Cent.	Pressure Blood-
		c.c. Vol.	Nitrogen gm.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.		
Ward	4/ 9/13	1,740	13.9	..	..	...	..	150
Ward	4/11/13	960	10.5					
Ward	4/12/13	1,020	11.1					
Ward	4/13/13	1,200	9.3					
Ward	4/14/13	1,530	9.5	30	14	3.0	13	160
High protein	4/16/13	1,440	9.9	..	..	...	..	139
High protein	4/17/13	1,560	12.2					
High protein	4/18/13	1,500	15.5	..	..	...	45	
High protein	4/20/13	1,920	18.3	37	20	2.9	33	140
Low protein	4/23/13	2,400	12.5					
Low protein	4/24/13	1,380	8.4					
Low protein	4/25/13	2,400	6.2					
Low protein	4/26/13	2,400	4.6					
Low protein	4/27/13	1,560	3.4	20	11	2.1	28	140
Average	....	.....	....	..	..	...	29.7	

from our figures, there clearly is no marked connection between the blood-pressure and the degree of retention; indeed, it is doubtful whether there is any connection. A high blood-pressure, therefore, does not necessarily indicate the desirability of introducing low nitrogen diets in nephritis. So far as can be seen at the present time, the only criterion available for regulating the protein content of the food in nephritis is the determination of the amount of retention by blood analysis. Five of the twelve patients (the last five) used in our experiments showed little or no abnormal retention of waste nitrogen, and there is no reason to doubt that these could take care of the protein contained in the usual hospital diet.

So far as the phenolsulphonephthalein test for the kidney efficiency is concerned, it is to be noted that there is no correspondence between the results of this test and the degree of waste nitrogen retention. Since it is possible to increase or reduce the retention by protein feeding one cannot expect any close agreement between it and the phenolsulphonephthalein test. The lack of correspondence is, however, probably not to be explained entirely on the basis of different levels of total protein metabolism.

In Table 13 we give the nitrogen elimination, the non-protein nitrogen and the phenolsulphonephthalein excretion — all in terms of the average for the first two periods of the experiments.

TABLE 13.—Average in Cases 1 to 12 of Urinary Nitrogen, Non-Protein Nitrogen and Phenolsulphonephthalein Excretion*

Case	Urine Nitrogen gm.	Blood Non-Protein Nitrogen, mg.	Phenolsulphonephthalein Excretion Per Cent.
9	8.0	28.5	27.0
3	8.7	37.5	33.5
2	8.9	44.0	26.2
5	9.2	54.0	19.8
7	9.7	61.0	28.0
1	9.8	40.0	31.6
6	10.3	50.5	30.0
10	10.9	30.0	28.0
8	11.0	29.0	29.0
11	11.4	31.0	29.5
12	12.3	33.5	29.7
4	14.3	48.5	46.6

* Average for first two periods arranged according to urinary nitrogen.

If 60 to 80 per cent. be taken as the normal elimination of 6 mg. of phenolsulphonephthalein excretion when injected intramuscularly it is clear that this elimination can be reduced by one-half or more before there need be any abnormal accumulation of waste nitrogen in the blood.

TABLE 14.—RESULT OF BLOOD TESTS IN CASES 13 TO 18

Case	Name	Age	Diagnosis	Blood									Phenol-sulphone-phthalein Excretion Per Cent. in 2 Hrs.
				Ward Diet			High Protein Diet			Low Protein Diet			
				Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.	Non-Protein Nitrogen mg.	Urea Nitrogen mg.	Uric Acid mg.	
13	*Patrick M.	63	Chr. interstitial neph.	92	70	3.5	124	109	4.5	..	..	...	8
14	Mary K. O.	75	Chr. interstitial neph.	42	34	2.5	61	41	3.5	..	..	...	54
15	Hannah J..	64	Chr. interstitial neph., aortic roughening, aneurysm of arch.	50	34	2.1	58	40	2.5	36	16	2.4	32
16	Mary K....	81	Chr. interstitial neph., cardiac hypertrophy, aortic roughening, mitral regurgitation	35	19	1.9	39	25	1.9	30	16	2.0	30
17	†Chas. M...	60	Chr. interstitial neph., epilepsy ...	34	19	2.6	69	55	2.0	23	11	...	25
18	Dennis O'B.	31	Chr. interstitial neph., albuminuric retinitis, alcoholic ...	58	41	2.0	‡75 80	52 62	2.1 2.5	41	20	2.1	6

* This patient died in "uremia" while on high protein diet two days after last sample of blood was taken.

† This patient was confined to bed during almost the whole period of experiment. Urinary nitrogen determinations made March 4 to April 4 showed nitrogen excretion varied from 22 to 15 gm. in twenty-four hours. Went on low protein diet, as given in first twelve cases, April 23. During a five-day period nitrogen excretion average in twenty-four hours was 5 gm.

‡ Taken one week apart.

It would seem from these results as though the direct determination of the non-protein nitrogen (and urea) in the blood furnishes a more reliable guide to what might be called the protein tolerance of patients than can be obtained from any "direct" test of kidney efficiency, for of all tests yet devised for this purpose the phenolsulphonephthalein test of Rowntree and Geraghty is admittedly the best.

In addition to the preceding experiments we have made a number of others which are less complete, but from which some noteworthy observations were obtained. These experiments were made before the series shown in Tables 1 to 13, and while in every case collections of urine were made it was suspected that in a number of instances the whole twenty-four-hour amount had not been saved. We, therefore, have not included our determinations of urinary nitrogen, but have been forced to rely on the dietary records kept by the nurses in charge.

As in the preceding experiments, eggs and meat were used in liberal amounts during the periods of high protein feeding. In the low protein periods, however, the patients were fed on cereals, bread and butter, vegetables and a little milk. The soluble starch employed so extensively in our later experiments was not used, so that in some cases it is to be feared that the calorific intake was too low.

UROBILIN: ITS CLINICAL SIGNIFICANCE *

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I. INTRODUCTION

The numerous studies made on urobilin and urobilinogen during the forty-four years since its discovery by Jaffé, while adding much to our knowledge of its chemistry and its clinical occurrence, still leave much to be desired as to methods for its estimation and as to its clinical significance. Some investigators are inclined to look on it still from the point of view of hemoglobin metabolism, while others consider it only in reference to hepatic insufficiency. Its relationship to the presence or absence of bile in the intestine has been a subject of considerable dispute, but in the main the contention of Friedrich von Müller, that it can originate only from the bacterial decomposition of bile reaching the intestine, is accepted. Nevertheless, the assertion of Fischler, that it can originate in the liver itself, seems to us probable. Whether it is then formed within the liver cell or is produced by decomposition of bilirubin in the biliary passages, it is impossible to state. A wide variability in point of view is reflected throughout the available literature. It has been our intention in entering on a study of this substance to endeavor to estimate its present value as an aid in diagnosis and prognosis, and we must frankly admit that it has been disappointing in some particulars, owing largely, perhaps, to the imperfections of the present methods of its estimation, and to its evident instability. Besides, when such variable factors as the bacterial fermentations within the intestine, the absorption from it, the activity of the liver, the elimination of bile, the eliminative power of the kidney, the rate of destruction of the red blood-corpuscles, the activity of the spleen, etc., have to be taken into account, it is not surprising that difficulty should arise in interpreting findings and in correlating the diverse views of many investigators and clinicians.

The interesting spectroscopic fluorescent and color tests for urobilin and its mother substance urobilinogen and their common occurrence in the body excretions, especially in disease, naturally stimulated much research as to their composition and origin and many clinical observations as to their significance. The Ehrlich aldehyd test, shown by

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Neubauer to be due to urobilinogen, received particular attention. The method of estimation with Citron's or other simple spectroscope of the urobilin and urobilinogen together proved with us to be fairly simple, and to lend itself readily to approximate quantitative studies based on the disappearance of the characteristic absorption bands between D and E, and B and F, with successive dilutions.

The term "urobilin" is not applied to a single body, but to a group of derivatives of blood and bile pigments containing the pyrrol nucleus. Throughout our work we have considered urobilin and its mother substance urobilinogen as practically the same, and have endeavored always to estimate them together in making clinical and experimental observations. The confusion between the two and the lack of a generally accepted theory of the origin of these substances is the cause of the present striking lack of uniformity in the interpretation of clinical and laboratory results.

The most prominent of the various theories as to the origin of urobilin are the hematogenous, the hepatogenous, the nephrogenous, the histogenic and the enterogenous. The latter is undoubtedly the most satisfactory, although it does not fully explain the origin of all urobilin within the body, for instance, that of some hepatic disorders (Fischler) and some cases of blood destruction and extravasation. In brief, these theories are as follows:

Hematogenous Theory.—This theory is that the urobilin can be, but is not necessarily, derived directly from blood pigment. It is based on the somewhat uncertain evidence of the long-known occurrence of urobilinuria in hemorrhage of the brain (von Bergmann), in blood extravasations (Kunkel), in extra-uterine pregnancy (Dick), in hemorrhagic ascites (such as the famous case of Gerhardt, in which there was also a carcinomatous closure of the ductus choledochus), after hemocytolytic processes, in sulphonal poisoning, in paroxysmal hemoglobinuria and in scurvy. While it is true that there is the possibility in many of these reported clinical observations of the existence of definite hepatic disturbance, still there is enough experimental evidence to warrant the assertion that at times urobilin can be derived directly from blood pigment without the intervention of either the liver or the intestine.

Hepatogenous Theory.—The principal tenet of this unsatisfactory theory is that there is failure on the part of the liver in its normal decomposition of hemoglobin, and that as a result of this insufficiency urobilin is formed and reaches the kidney through the blood-stream and is there eliminated, or is added to the intestinal contents by the bile. A somewhat strict interpretation of this theory is that there is a direct formation of urobilin within the liver cell, or at least within the bile passages from the bile pigment.

Nephrogenous Theory.—In brief, this is based on the fact that urobilin as such is very rarely found in the blood, and that it reaches the kidney in the form of bilirubin, which is reduced to urobilinogen in its passage through the renal epithelium. Herscher states that kidney substance can reduce bilirubin, but surviving kidneys with bilirubin circulating in their blood secrete no urobilinogen, but only bilirubin in the collected urine. The principal argument against this theory is that urobilin does not occur in many cases of jaundice.

Histogenic Theory.—This theory that hemoglobin or bile pigments are reduced in the tissues to urobilin and then reabsorbed and eliminated, offers an insufficient explanation of the various known phenomena.

Enterogenous Theory (Friedrich von Müller).—While not meeting all conditions, this theory is based on the explanation of the established facts of urobilin formation. In brief, it is based on the finding that bile pigment reaching the intestinal lumen undergoes a change into urobilinogen and urobilin caused by bacterial decomposition. It may then be absorbed into the capillaries of the portal system and so reach the liver parenchyma. If the liver is normal the major portion of the urobilin is broken up or synthesized to bile or blood pigment. A portion may be secreted in the bile and so be returned to the intestinal lumen to be reabsorbed or passed off with the stool. When the liver parenchyma is damaged, these changes in the urobilin may not take place, but it passes on into the general circulation. It reaches the kidney through the blood and is eliminated in the urine. This theory is principally sustained by the absence of urobilin in the urine in any quantity in cases of obstruction of the common duct.

We shall not stop for a complete discussion of these theories, since points of view vary, and there is no common agreement at present. We can safely assume that as a rule the presence of urobilinuria is indicative of the fact that bile is reaching the intestine, and that large amounts of urobilin in the urine usually mean that there has been either abnormal destruction of red blood-corpuscles, or an insufficiency of the liver to perform its normal functions. A large amount of urobilin in the stool indicates increased blood destruction. Urobilinuria frequently disappears in severe diarrhea. Although urobilin is normally present in the urine in small quantities, its presence cannot be ascertained by the ordinary qualitative tests — a positive reaction with Schlesinger's zinc acetate test or Ehrlich's aldehyd test is not found in normal urine. It is increased in many pathological conditions. It is commonly increased in infectious diseases, in diseases in which there is wide-spread hemorrhage, traumatic or otherwise, in pernicious anemia, malaria, cardiac decompensation, various forms of liver and gall-passage disease, and in numerous intoxications such as those due to alcohol, chloroform, lead and carbon monoxid.

II. SUMMARY OF QUANTITATIVE METHODS FOR UROBILIN ESTIMATION

Following is a summary of only the most essential points of the methods which have been used:

Almost all the work done has been with the urine. The methods may be divided roughly into those requiring a separation of the urobilin from the urine by means of precipitation with ammonium sulphate; secondly, those depending on the spectroscopic absorption bands of urobilin, and thirdly, those based on the property of fluorescence and lastly colorimetric methods depending on the violet color produced by copper sulphate in urobilin solutions.

1. Methods Involving Salting out of Urobilin by Means of Ammonium Sulphate.—Hoppe-Seyler in 1891 estimated urobilin in urine gravimetrically. The acidified urine was saturated with ammonium sulphate, and the precipitate extracted with chloroform and alcohol. The solution was evaporated, the residue dissolved in ether, filtered and evaporated, and the residue dissolved in alcohol, evaporated and weighed.

Viglezio in the same year recommended a method which depended on the salting out of the urobilin with ammonium sulphate and its solution in alcohol. The amount was gaged by noting how much of this solution was required to produce a certain grade of fluorescence or the appearance of the spectroscopic absorption bands, when it was added to a solution of zinc chlorid.

Studenski added copper sulphate to the urine, precipitated with ammonium sulphate and dissolved the copper compound of urobilin in chloroform. This color was compared with that produced by copper sulphate in a solution of urobilin of known strength.

Ladage recognized the necessity of taking the urobilinogen into account and recommended that iodin should be added to convert it to urobilin. The urobilin was then precipitated by saturation of the urine with ammonium sulphate, and the acid chloroform solution diluted until the spectroscopic absorption became invisible. In Fr. Müller and Huppert's method a mixture of barium chlorid and barium hydrate is added to the urine, and the precipitate is filtered off and washed with hot water. The excess of barium in the filtrate is removed by sodium sulphate, and the filtrate after neutralization with sulphuric acid is saturated with ammonium sulphate. The precipitated urobilin is filtered off, allowed to dry in the air and extracted three times after acidification with a warm mixture of alcohol and ether. This solution is then evaporated to a convenient bulk and the amount of urobilin estimated spectrophotometrically.

Charnas in 1909 gave us an alternative method to one based on the spectroscopic characteristics of urobilin, a gravimetric method in which after all urobilinogen in an ether extract of the urine has been converted into urobilin by exposure to sunlight, the urobilin is separated by water from the ether, and after filtration precipitated by ammonium sulphate, dried, dissolved in alcohol, the alcohol evaporated *in vacuo* and the residue weighed.

2. Spectroscopic Methods.—Gerhardt (1889) and Beck (1895) made estimations by means of the spectrophotometer using Vierordt's tables of the grade of light extinction in different regions of the spectroscope in normal urine and solutions of urobilin.

Saillet (1897) extracted the freshly passed urine with acetic ether. In another specimen the urobilinogen was converted into urobilin by exposure to light and then extracted. The two extracts are added together and diluted until the spectroscopic band disappears.

Conner and Roper (1908) made approximate measurements of the amount of urobilin in urine by noting the number of dilutions required to obliterate the urobilin band in the urine. They recommend the addition of a few drops of Lugol's solution to the urine in order to convert the urobilinogen into urobilin.

Auche (1909) found that a solution of urobilin of 1 : 200,000 prepared by a method he describes is sufficient to make the five absorption bands of potassium permanganate all of equal intensity, although without it some are lighter than others. He therefore superimposes the urine, which in some cases has to be extracted with a thymol-chloroform solution, over a solution of potassium permanganate, and dilutes the urine or its extract until all the bands are of equal intensity.

Simpson (1910) acidifies the urine with sulphuric acid and exposes it to light for some time in order to convert urobilinogen to urobilin. It is then diluted until the urobilin band disappears. This method gave fairly accurate results when a dilution of fifteen or more volumes was necessary. With smaller amounts the reading was apt to be obscured by other pigments.

Hausmann (1913) adds copper sulphate to the urine and dilutes until the spectrum becomes invisible.

Henocque, Hayem, Gautretet, Deniqués, Hildebrandt, Riva and Zoja have used one modification or another of these spectroscopic methods.

Charnas (1909) makes the urine alkaline, allows it to ferment at 37 C. (98.6 F.) for from twenty-four to forty-eight hours, acidifies with tartaric acid, and extracts with ether and petroleum benzin. To a portion of the ether extract an ethereal solution of paradimethylamidobenzaldehyd is added and two to three drops of absolute alcohol saturated with hydrochloric acid gas. After dilution if necessary with alcohol a spectrophotometric reading is made.

3. Methods Depending on the Property of Fluorescence.—Grimm (1893), Fischler (1906), Grigant and Monod (1909), and Descomps (1909) gage the amount of urobilin by the intensity of the fluorescence present in the zinc salt filtrate of the urine. Various devices are adopted to aid the conversion of urobilinogen into urobilin.

4. Colorimetric Methods.—Bogomaloff (1892) used a colorimetric method depending on the depth of the red-violet color produced in a chloroform extract of urine containing urobilin by the addition of copper sulphate.

Braunstein (1903) used a modification of this method.

Flatow and Brünell (1913) estimate the amount of urobilinogen in fresh urine from the depth of the red color given on the addition of Ehrlich's reagent. As a standard they use a phenolphthalein solution to which a few particles of metallic sodium have been added.

Brugsch and Retzlaff (1912) modify Charnas' method by extracting the alkaline urine first with ligroin. They make the final reading with Plesch's colorimeter, using a solution of Bordeaux red as the standard.

The Stools

Quantitative estimations of urobilin in the stools have been carried out by comparatively few investigators. Gerhardt at first used a somewhat complicated process of extraction and purification but later except in special cases simply extracted with acid alcohol and read spectrophotometrically. Auche extracts with alcohol, removes other pigments by shaking with ligroin and thereafter makes the same spectroscopic determination as he employs in urine extracts.

Simpson (1910) mixes the day's feces with water and adds enough dilute sulphuric acid to make the mixture distinctly acid. For one or two days full exposure to light is allowed to convert the chromogen into urobilin. Filtration is then carried out and the residue repeatedly extracted until the filtrate becomes colorless. Direct examination of the filtrates is made and the amount determined from the degree of dilution required to obliterate the spectroscopic band.

Brugsch and Retzlaff (1912) attempt to convert all the urobilin into urobilinogen by allowing the stools to stand for some time before extracting with ligroin to remove indol derivatives and then with acetic ether. After the addition of paradimethylamidobenzaldehyd they make a colorimetric determination as in their method with urine.

Serum

No quantitative work has been done with serum. The methods employed for the detection of urobilin in serum were reviewed by Conner and Roper. We shall refer therefore only to those which have appeared since their publication.

Morel and Monod (1908) add alcohol to the serum and heat to boiling for half an hour. The filtrate is concentrated and a drop of Obermeyer's reagent and an alcoholic solution of zinc acetate and acetic acid are added. After twenty-four hours the filtrate is examined for fluorescence.

Auche (1909) adds a solution of iodin in potassium iodid to the serum and afterward some zinc cyanate in ammonia and filters. The filtrate is examined spectroscopically.

Fromholdt and Nersessoff (1912) precipitate the oxalated plasma with alcohol, filter, concentrate, acidify, and shake with amyl alcohol, and then with alkaline water. The water is then made acid and shaken with amyl alcohol and examined spectroscopically.

III. DISCUSSION OF METHODS

In reviewing the literature on these methods, it was evident that the one main difficulty encountered by all investigators was the problem of separating urobilin and urobilinogen from the other coloring matters present in the excretions without at the same time destroying more or less of it. Many had frankly given up the attempt to attain any but the roughest purification, and had relied on the intensity of the physical properties of fluorescence or of light absorption. In doing so they had, of course, confessed that their results were not quantitatively accurate, for variations in the impurities present would undoubtedly affect the basis on which their determinations rested. Others have not remained satisfied with this, but have attempted to attain at any rate approximately pure solutions before estimation.

The question as to which of these two methods produced the better result depended on whether more was gained in accuracy than was lost by destruction of urobilin in the various precipitations, separations and evaporations required.

It appeared to us that there was one way in which the question could be answered. When undiluted urine is examined spectroscopically, nothing is seen, as a rule, except a general absorption of light, which becomes deeper and deeper toward the blue end of the spectrum. Even if urobilin is present, the absorption band cannot be clearly differentiated. When the amount of urobilin, however, is much larger than the other light-absorbing substances present, one finds that on simple dilution with water the band between E and F becomes more and more distinct, so that it at last stands out sharply. On still further dilution it begins to fade, and a more or less definite point is reached at which it becomes invisible when the full amount of light is allowed to pass through the spectroscope, but can still just be seen when the light is diminished. In some urines one may have to carry the dilution to forty or more times the original volume of urine to reach this point. At this dilution the disturbing effect of other substances is negligible. Such urines afford an excellent means of deciding as to whether any particular manifestation leads to a loss of urobilin or not, because the number of dilutions required to remove the urobilin band before and after the procedure can be very readily determined. We were fortunate at this time in having under observation for several months a patient with bronzed diabetes in whose urine unusually large amounts of urobilinogen and urobilin were constantly present.

Practical experience with this method very quickly showed us that any and every tried means which may be applied to separate urobilin from the urine was associated with more or less loss. Extracts from precipitations with ammonium sulphate, separations by ether, chloroform or thymol-chloroform solutions, and processes of evaporation, with or without heat, all led to a greater or less diminution of the spectroscopic dilution value. Such methods are applicable in the endeavor to obtain pure urobilin, but it seems to us that they can have no place in any quantitative estimation, for the amount destroyed is too variable and too incapable of control. The one salient fact which has to be kept constantly in mind in choosing a method of estimation is that almost any manipulation is apt to be associated with more or less loss of urobilin. It is better to recognize from the first that ordinary chemical methods are not applicable to a substance which is so labile, and that their employment gives only a fallacious appearance of accuracy. Any gravimetric method for this reason seems to us to be entirely out of question. Solutions of urobilin or urobilinogen may no doubt be obtained in a state of sufficient purity to admit of spectrophotometric determination, but with the means which have hitherto been employed for this purpose the error by loss so far outweighs any increase of accuracy in the final determination as to make results obtained by such methods of very doubtful value.

Yet in the case of all urines in which the amount of urobilin was not exceptionally large and in dealing with stools, some preparation was necessary, for no direct reading could be made. After trying a large number of procedures, the conclusion was reached that the most innocuous of all was to mix equal parts of urine and a saturated solution of zinc acetate in alcohol and to filter. This is Schlesinger's qualitative test for urobilin. A small amount of urobilin may be absorbed by the precipitate, and at first we filtered under pressure and washed the precipitate with alcohol; but latterly we have found that the error is so small compared with other unavoidable sources of error that in routine clinical examinations we have simply taken the first fraction of the filtrate.

Another necessary procedure also soon became apparent. It has, of course, long been known that on adding acid to a urobilin solution the position of the absorption band is altered, but we had not gathered that the intensity was changed to the extent which we found in many urines.

Sometimes the increase in the number of dilutions required to obliterate the band was ten times as great in filtrates which had been made strongly acid as in the fresh filtrate. It was obvious that unless constancy could be attained in this point, no results of value could be obtained. The intensity of the spectroscopic characteristics of urobilin are as dependent on reaction as is the property of fluorescence. The difference is that to attain maximum fluorescence a nice balancing of reaction is required, whereas the strongest absorption band is obtained in a strongly acid solution and an excess of acid does no harm. All that is required, therefore, is to be sure that enough acid is present. For this reason alone the spectroscopic methods are to be preferred to those based on fluorescence in which large errors may arise from slight variations in reaction.

Still another essential point in any method is that the urobilinogen as well as the urobilin shall be taken into account, and that if possible the quantitative relationship between the two bodies shall be established so that the result can be expressed as a single figure. Urobilin is simply an oxidation product of urobilinogen; from the clinical or physiological points of view they have exactly the same significance. Urobilinogen is potential urobilin. In any specimen of urine or stool the relative amounts of the two are constantly changing, the amount of urobilin increasing and of urobilinogen decreasing the longer the exposure to light and air. In some methods this difficulty is met by keeping the extract for twenty-four hours exposed to light, and it is assumed that all the urobilinogen will then have been converted into urobilin. Others endeavor to hasten the process by the addition of oxidizing agents, and one method takes the opposite course, and by alkaline fermentation, attempts to convert all the urobilin into urobilinogen.

The only way by which urobilinogen can be determined, except gravimetrically, is by the spectroscope through the absorption bands of the pigment produced by its reaction with paradimethylamidobenzaldehyd. We used a solution containing 20 gm. in 300 c.c. of 50 per cent. concentrated hydrochloric acid. One c.c. was added to every 10 c.c. of the alcoholic zinc acetate filtrate. This gave a sufficient amount of acid to produce the maximum intensity in the urobilin band and at the same time brought out the urobilin spectrum, so that the dilution values of both urobilin and urobilinogen could be read in the same filtrate. The amount of urobilinogen could then be expressed as representing so many dilutions in the same way as with the urobilin.

The first point investigated was the effect of light on urobilinogen. It was found to vary greatly with the intensity of the light. A few hours' exposure to direct sunlight suffices to cause the complete disappearance of urobilinogen. With indirect light the process required a longer time: but after exposure to a diffuse light in a room with ground-glass windows, there was found after twenty-four hours to be an almost complete disappearance of urobilinogen. The figures in Table 1 show the effect of leaving the zinc acetate filtrates of urine in diffuse room-light for twenty-four hours.

TABLE 1.—EFFECT OF LEAVING ZINC ACETATE FILTRATES OF URINE IN DIFFUSE ROOM-LIGHT FOR TWENTY-FOUR HOURS

Urobilinogen

Filtrate Examined at Once	Examined After 24 Hours in Room-Light
32	1
37	0
45	2
25	0
21	1
12	0
7	0
16	0
34	0
40	1
18	1
25	0
19	0
40	0

The effect on urobilin of a similar exposure to light could not be determined in the same way, since all fresh urine and stools contain urobilinogen which passes over in part at least to urobilin. It was invariably found, however, in these specimens in which by various means the urobilinogen had been removed, that light had a destructive effect on urobilin, as was shown by the diminution in the dilution value after exposure.

Under the influence of light, as the urobilinogen diminishes the urobilin increases. The question remained, however, as to how much loss of urobilinogen and urobilin occurred during this process. The precise degree of loss could be found only if we knew the quantitative relationship between urobilinogen and urobilin and the relative light-absorbing powers of the urobilinogen and urobilin pigments. These facts are not known, but an indication of the amount of loss of urobilin was gained by comparing the total dilution value obtained by adding together the urobilinogen and urobilin values in the fresh filtrates, in those which had been in darkness for twenty-four hours and in those which had been left in diffuse room-light for the same time.

After twenty-four hours in darkness there had been a diminution of urobilinogen from 371 to 301 and an increase of urobilin from 6 to 134. The light-absorbing power of urobilin must then either be greater than that of the urobilinogen pigment, or one molecule of urobilinogen must break up into two or more molecules of urobilin. In any case there is an increase of the total dilution values for urobilinogen and urobilin together, associated with a diminution of urobilinogen and an increase in urobilin.

TABLE 2.—Quantitative Change in Urobilinogen and Urobilin Under the Influence of Light

Fresh Urine		After 24 Hours in Dark		After 24 Hours in Room-Light	
Urobilinogen	Urobilin	Urobilinogen	Urobilin	Urobilinogen	Urobilin
32	2	28	11	1	26
37	0	30	12	0	32
45	0	40	12	2	37
25	0	22	8	0	17
21	0	19	14	1	16
12	2	10	7	0	3
7	2	6	3	0	5
16	0	14	7	0	15
34	0	30	12	0	21
40	0	35	13	1	30
18	0	14	10	1	16
25	0	14	9	0	16
19	0	7	4	0	8
40	0	32	12	0	24
371	6*	301	134†	6	266‡

* Total "Urobilin" 371 + 6 = 377.
† Total "Urobilin" 301 + 134 = 435.
‡ Total "Urobilin" 6 + 266 = 272.

In the filtrates exposed to light there is more than forty times as much urobilin as in the fresh filtrates and twice as much as in those kept in the dark, and yet in spite of that the total dilution value is much less, only 266 as compared with 377 and 435. If for a moment it is assumed that the diminution of urobilinogen and increase in urobilin in the filtrates kept in the dark represent the relationship between the two bodies, then 371 — 301 = 70 of urobilinogen should produce 134 — 6 = 128 of urobilin. But the disappearance of 371 — 6 = 365 of urobilinogen in the filtrates exposed to light led to an increase of only 266 — 6 = 260 of urobilin instead of the 667 which should have resulted. It is impossible to explain this decrease in total dilution value except as due to a destruction of part of the urobilinogen or urobilin or both. Since the actual amount of urobilinogen or urobilin destroyed by exposure to light cannot be calculated, and varies so greatly with different degrees of intensity of light and with other unknown conditions, the conclusion was reached that it was not a means which could be used in any quantitative method to convert urobilinogen into urobilin, and that as far as possible exposure to light should be avoided in urobilin estimations.

Attention was then turned to the effect of oxidizing agents which have been recommended especially by French investigators; but here also the results were disappointing, for those reagents which were effective in oxidizing the urobilinogen were also very destructive to the urobilin.

Charnas states that if urine is made alkaline and left for from twenty-four to forty-eight hours in the incubator, all the urobilin will be converted into urobilinogen, which can then be estimated by the spectrophotometer. It is noteworthy that Charnas does not give any estimations indicating the decrease of urobilin and increase of urobilinogen during the process, nor does he bring forward any evidence to show whether or not any part of the urobilinogen or urobilin is destroyed by the fermentation which occurs. It has long been known that in freshly passed urine urobilinogen is present alone or at any rate in far greater amount than urobilin, suggesting that as it is excreted through the kidneys it is all in the form of urobilinogen; and it has been the universal experience that the longer a urine is kept the less urobilinogen will be found in it, so that the statement that in alkaline urine left exposed to the air at a temperature of 37 C. the reverse process occurs, and that instead of an oxidation a reduction takes place, is not one which can at once be accepted. We know that in the intestine there is a reduction of urobilin to urobilinogen, but there conditions are present much more favorable to reduction processes than those which are present in urine left exposed to air. Outside the body the formation of urobilin constantly goes on; but to bring about the reverse process the strongest reducing agents we know have to be employed. It seemed to us, however, that the question was one which could be decided by the simple spectroscopic method we have outlined.

Readings of the relative amounts of urobilin and urobilinogen in thirty specimens of urine before and after alkaline fermentation at 37 C. were made. In most of the cases fermentation was allowed to continue for twenty-four hours. The first twelve results are given in Table 3.

TABLE 3.—UROBILIN AND UROBILINOGEN BEFORE AND AFTER ALKALINE FERMENTATION AT 37 C.

Before Fermentation		After Fermentation	
Urobilinogen	Urobilin	Urobilinogen	Urobilin
15	5	0	11
12	0	0	9
26	9	7	0
15	5	0	0
12	0	6	0
7	0	8	3
26	9	0	2
19	3	5	2
0	3	0	11
0	5	30	0
17	6	0	1
10	5	50	2

Of these thirty specimens there was a diminution instead of an increase of urobilinogen after fermentation in all except three. In two there was a very considerable increase of urobilinogen, but both these specimens contained some bile, and as we found that urobilinogen was produced in decomposing bile we are inclined to ascribe these exceptions to this cause.

It seemed that these results, so completely at variance with the statement of Charnas as to the effect of alkaline decomposition in urine, might be due to the urobilinogen having become absorbed in the heavy deposit of phosphates in the fermented urines. The experiment was therefore repeated in ten urines, the readings before and after fermentation being made after the specimns which had been made faintly alkaline with ammonium carbonate had again been made acid with tartaric acid. Before fermentation a total reading of urobilinogen 18 and urobilin 27 was made. After twenty-four hours' fermentation, urobilinogen 13 and urobilin 16 was recorded, and after forty-eight hours, urobilinogen 12 and urobilin 4. We must conclude then that alkaline fermentation in the dark at a temperature of 37 C. not only does not quantitatively convert urobilin into urobilinogen, but that it has a directly destructive action on both.

Since there was no available way of converting all the urobilinogen into urobilin or vice versa, the only alternative was to make estimations of each separately. But could such results be added together and expressed by a single figure? Our knowledge of the chemistry of these bodies is not yet sufficiently advanced to enable us to be sure that one or the other may not be a condensation of the other so that one molecule of urobilinogen, for instance, may break up into two or more molecules of urobilin. No idea as to the relationship between them could be gained by noting the degree of increase in the dilution value of urobilin which followed a decrease in urobilinogen, for the factors concerned are too complex and variable to allow of any true idea being obtained in this way. For while the urobilinogen is being converted into urobilin, both are undergoing other changes and are losing the spectroscopic characteristics on which our determinations rest. In preparations of urobilin and urobilinogen made from bilirubin by Fromholdt's method we found such a lack of relation between the weight of bilirubin and the weight of urobilin produced, and such a variability in the relative amounts of urobilin and urobilinogen formed, that it did not seem likely that in this way either could we successfully determine whether or not urobilin and urobilinogen were equivalent in value. In dealing with two such extremely unstable substances whose presence can be detected only by a single physical property and which are constantly changing into other bodies which we have no means of estimating, the problem of their exact relationship is one whose solution will probably not be definitely established until we have more knowledge of the decomposition products of hemoglobin. For urobilinogen and urobilin are only links in the chain of hemoglobin derivatives; they cannot be regarded as final end-products. The problem which we were attempting to solve was not the exact quantitative determination of urobilin, however, but simply the question as to whether or not any information of clinical value could be gained from urobilin estimations, in spite of the errors necessarily involved in any of the present methods. With this end in view the best that could be done was to add together the dilution values of urobilinogen and urobilin. We do not know that they are equivalent, but, on the other hand, we know that they are not very different in value. The proportion of the two substances varies so much in different specimens of urine, stool and bile that no comparison can easily be made if the dilution values for each are given separately.

As a result of this preliminary review we determined that the best method would be one which avoided all but absolutely essential manipulation of the material, one which was based on the most characteristic of the properties of urobilin, the spectroscopic absorption bands, and one in which the attempt to convert all the urobilinogen into urobilin or vice versa was abandoned and the results of separate estimations of the two were simply added together. Throughout this paper when the term "urobilin" is used apart from "urobilinogen," the sum of the dilution values of urobilin and urobilinogen is intended.

The following are the details of the methods which we finally adopted:

IV. METHODS

Urine

The method of collection of the twenty-four-hour urine has a considerable effect on the total spectroscopic reading. The vessel in which the urine is collected should be of dark brown glass and should be kept in darkness. Thymol crystals should be added, for even in cases in which no obvious fermentation had occurred we sometimes found a diminution in the total amount if no preservative was present. After measuring the amount of the twenty-four-hour urine, 10 c.c. are mixed with 10 c.c. of a saturated alcoholic solution of zinc acetate, and after a few minutes filtered. If a number of urines are being examined at the same time it is convenient to have test-tubes graduated to 10 and 20 c.c. Ten c.c. of the filtrate are taken and 1 c.c. of Ehrlich's solution[1] is added. It was found that this amount produced a sufficient concentration of acid in the mixture to give the maximum intensity of the urobilin band and contained enough of the paradimethylamidobenzaldehyd for the reaction with urobilinogen. The development of the urobilinogen band is not instantaneous. We found that as a rule it had attained its full intensity in a quarter of an hour. The action can be greatly accelerated by heating, but this is to be avoided. It is better to wait for an hour before making the reading, and during this time the solution should be kept in the dark. After three or four hours there is a diminution of the urobilin and urobilinogen in filtrates from urines, so the estimation should be made not later than three hours after adding the Ehrlich solution. We found that Citron's hand spectroscope[2] was the most convenient instrument to use. The filtrate was washed into a graduate and diluted with tap-water until first one and then the other bands of light absorption had disappeared when the full amount of light entered the spectroscope, but were still visible when the light was partly shut off. This gives a fairly definite end-point, and we did not find any great variation in the readings made by different persons. It is important of course that the light shall be always of approximately equal intensity. We made the readings in a dark room with a Tungsten electric bulb, holding the spectroscope close to the source of light. In highly colored urines one may be in doubt as to whether or not a trace of urobilin is present, for there may be so much general absorption of light as to obscure the urobilin band in the undiluted filtrate. There is no such difficulty with the urobilinogen band which lies between the red and yellow where there is no marked light absorption. With urines containing bile, if the amount of urobilin is not very large, it is necessary to add some fullers' earth and to leave the mixture standing for some time before filtration. If this is done the urobilin band can usually be read even in the undiluted filtrate. The dilution required gives the value for 5 c.c. of urine. If this figure is multiplied by the number of 5 c.c. quantities in the twenty-four-hour urine, the number of dilutions which would have been necessary if all the urobilinogen and urobilin in the twenty-four-hour amount had been concentrated in a volume of 5 c.c. is obtained. For instance, if in a twenty-four-hour urine measuring 1,000 c.c. a reading of ten dilutions for urobilinogen and of twenty for urobilin were made, the total urobilin would be 30 x 200 = 6,000. We tried to determine the dilution value of definite weights of urobilin prepared from bilirubin, but different preparations varied so much in their dilution value that it was obvious that we were not dealing with pure urobilin and we abandoned any attempt to express our results in milligrams of urobilin.

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[1] Paradimethylamidobenzaldehyd, 20 gm.; concentrated hydrochloric acid, 150 c.c.; water, 150 c.c.

Stools

All the feces passed in the twenty-four hours were collected in the same receiver, the stools being protected from light. They were then washed into a large graduate and thoroughly ground up with water into a homogeneous paste, and water added to 0.5, 1, or if necessary 2 liters, depending on the quantity of stool. After thorough mixing, 25 c.c. were taken and 75 c.c. of acid alcohol (95 per cent. alcohol, 1,600 c.c.; concentrated hydrochloric acid, 25 c.c., and water, 800 c.c.) were added. The mixture was then put into a shaker for about half an hour. A considerable number of extractives were tried for removing the urobilin from the stools, but none were found so efficient as alcohol with hydrochloric acid. After thorough mixing in the shaker an equal quantity of a saturated solution of zinc acetate in alcohol was added and the mixture was filtered. After adding 2 c.c. of Ehrlich's reagent to 20 c.c. of the filtrate, the solution was put aside in a dark place until next day. The addition of zinc acetate is not absolutely essential, but in some cases we observed an intensification of the urobilin band following its use, and it is perhaps an advantage to make the urine and stool readings as far as possible under the same conditions. The development of the urobilinogen band was not always complete until six hours had elapsed, but thereafter there was no loss of urobilinogen or urobilin for a long time, although this was not the case with the zinc acetate filtrates before the addition of Ehrlich's solution. The reading was made in the same way as with the urine and the total amount calculated for the volume of stool after grinding up with water, the dilution of the 25 c.c. by acid alcohol and zinc acetate being taken into account. Instead of using tap-water for dilution of the final extract, 60 per cent. alcohol was required to avoid the development of a precipitate.

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[2] This can be obtained from Paul Altmann, Luisenstrasse, Berlin, Germany.

Bile

A measured amount of bile was mixed to a paste in a mortar with fullers' earth and left for some hours. An equal amount of the alcoholic solution of zinc acetate was then added and the mixture filtered under pressure, and the remainder washed with measured amounts of zinc acetate alcohol. In this way almost all of the bilirubin was absorbed, and though no doubt there was some loss of urobilinogen and urobilin, the comparatively small amounts found in the washings compared with the quantities present in the first filtrate seemed to indicate that the fullers' earth had very much less capacity for absorbing urobilin than bilirubin. Small amounts of urobilin or urobilinogen could no doubt be overlooked by this method. The Ehrlich solution was added in the same proportion as in the urine, but the dilutions had to be made with alcohol instead of water.

Blood-Serum

We have tried various methods, but so far we have not been successful in demonstrating urobilin with certainty.

V. THE EXCRETION OF UROBILIN IN URINE

Urobilin is a normal constituent of the urine, but the amount is so small under ordinary conditions that it can be demonstrated only by extracting large quantities of urine.

With the methods we have used, a positive result in twenty-four-hour specimens of urine indicates an abnormal increase over the amount usually present. We have only very rarely been able to find a faint and doubtful degree of absorption in the region of the urobilinogen or urobilin bands in the urines of persons in apparent health. When, therefore, urobilin is spoken of as being absent from urine, it is understood that an absence of an increased amount of urobilin is meant.

Saillet found in two normal persons that the quantity of urobilin excreted during the eight hours of sleep was only about one-tenth of the total twenty-four-hour amount. He gives two curves of the excretion during the daytime which show some relation to the body-temperature variations. He suggests a connection with the processes of digestion and of general metabolism.

In a case of bronzed diabetes with a large urinary excretion of urobilin, we had an opportunity to study the excretion from hour to hour. The patient was on a von Noorden strict diet plus 50 gm. of bread. His habits were very regular. He rose at 7 a. m. and went to sleep at about 9 p. m. Urine was passed every two hours during the daytime, and the amount of urobilin determined at once. The amount passed during the six or eight hours of sleep was kept in the dark and the urobilin determined at the earliest opportunity. In such freshly passed specimens, practically all the urobilin is in the form of urobilinogen, and the probable error arising from the assumption that the urobilinogen and urobilin readings represent equivalent values is avoided. For over a month, the two-hourly excretion was determined every day, with the result that there was invariably found to be a marked diminution in the amount excreted at night. A graphic representation of the excretion during three consecutive days is given in Chart 1. The chart is typical of the results throughout the whole period. It shows the decrease of urobilin in the night urine and the great variation in the quantity from day to day and from hour to hour. The only constant feature is the fall during the night. Otherwise there is complete irregularity and the hour of maximum elimination occurred at any time during the day.

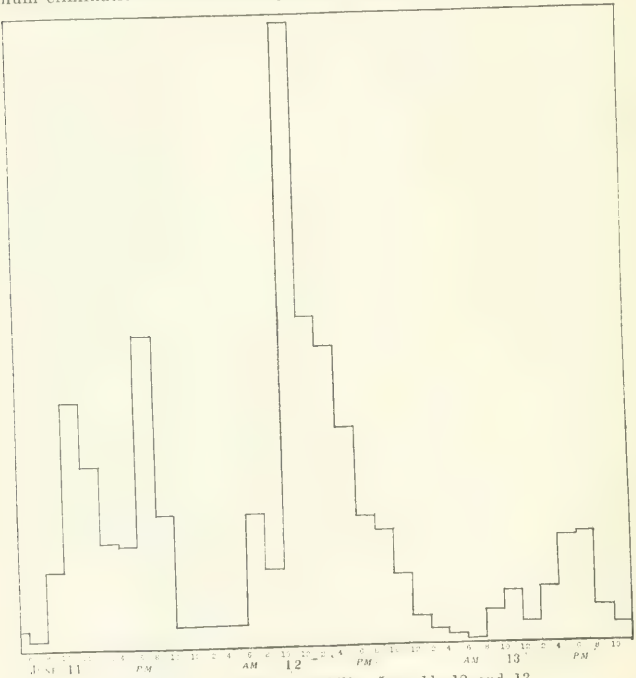

Chart 1.—Excretion of urobilin, June 11, 12 and 13.

When the patient remained up and took his meals during the night and slept in the daytime, the amount excreted in the night was much larger than in the day.

Charts 3, 4, 5, 6 and 7 show the relation between the excretion of water, total solids, sugar, chlorids and urea and urobilin. The relation was only a very general one, for the urobilin excretion shows irregular and wide fluctuations.

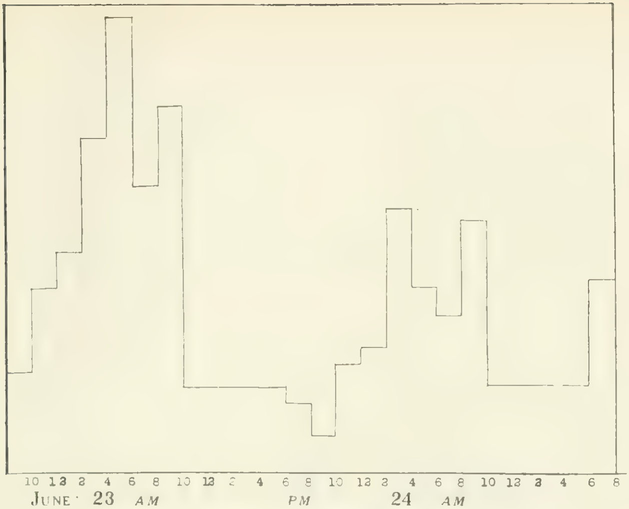

Chart 2.—Excretion of urobilin, June 23 and 24.

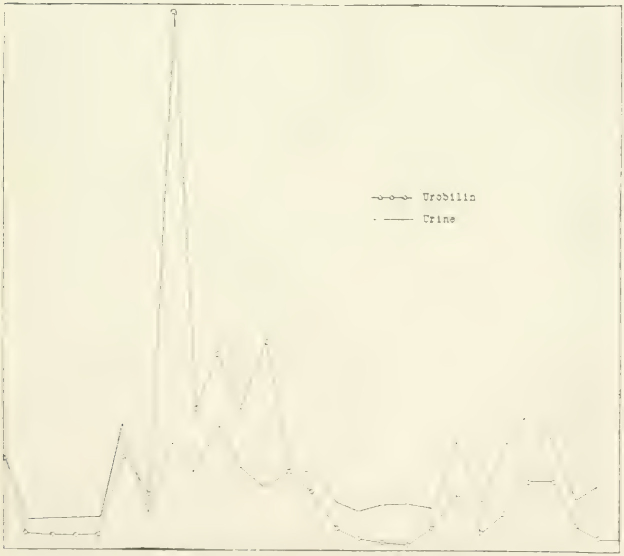

Chart 3.—Volume of urine and urobilin.

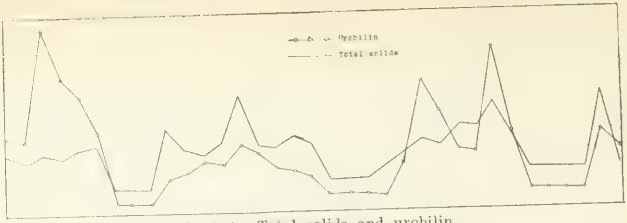

Chart 4.—Total solids and urobilin.

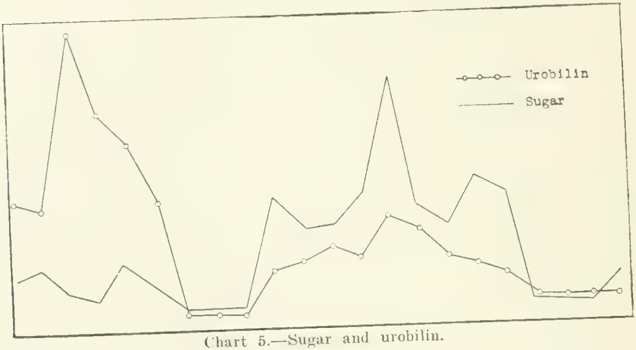

Chart 5.—Sugar and urobilin.

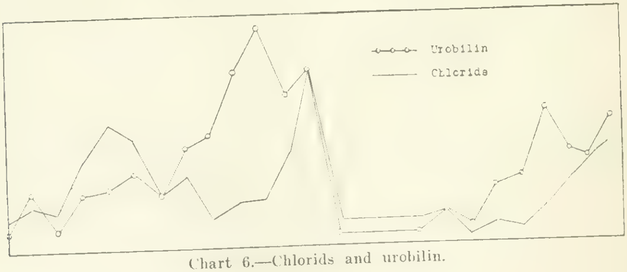

Chart 6.—Chlorids and urobilin.

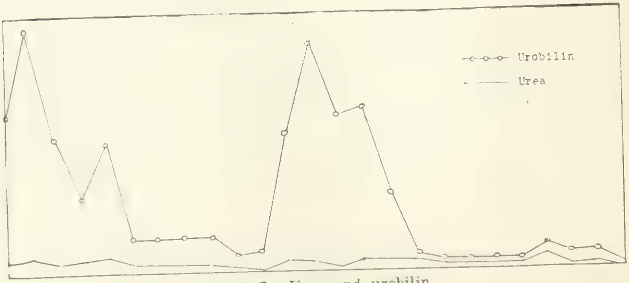

Chart 7.—Urea and urobilin.

These results appear to us to be of interest in connection with the question of urobilin excretion by the kidneys. It is generally agreed that most of the urobilin is formed in the intestine and is carried by the portal vein to the liver. There it is supposed to be either broken down further or resynthesized to bilirubin or hemoglobin (Brugsch) except for a very small part which is carried into the general circulation and is excreted through the kidneys. When the liver is diseased, the destruction or rebuilding of urobilin fails more or less, so that a greater quantity of the urobilin absorbed from the intestine passes by the liver to the kidneys.

The wide fluctuations in the quantities of urobilin in this case can scarcely be due to variations in the amount of absorption from the intestine. It is true that bile enters the duodenum only at intervals, but they are regular intervals when the periods of digestion are regular, and on these charts no signs of any periodicity during the daytime can be traced. In any case, the bile passes through the small intestine in about four hours, and as our findings as to the amount of urobilin in various parts of the intestinal tract show, the greatest quantity of urobilin is in the large intestine, not in the small. Urobilin is always present in the large intestine, and from this situation one could not expect any considerable changes from hour to hour in the amount absorbed. Urobilin is a readily diffusible substance, and since water is removed from the large intestine, it seems probable that urobilin will also be taken up by the blood.

Nor does it seem that changes in the excretory functions of the kidneys can account for more than a small part of the urobilin variations. The amounts of sugar and chlorids fall during the night mainly because their absorption from the alimentary tract almost ceases and not because there is any marked decrease in the eliminating functions of the kidneys. But urobilin is present in the large intestine in as large amount during the night as during the day, and if absorption is uniform one would expect uniform excretion, or at least no greater variation than might be ascribed to alterations in the circulatory and nervous mechanism of the kidneys. We have no evidence of any specific diminution in excretory power of the kidneys for any substance during the night.

If the absorption and excretion of urobilin appear to be too continuous and uniform to explain these charts, can we regard the variations shown in them as indicative of fluctuations in the power of the liver to keep the urobilin reaching it from the intestine from entering the general circulation?

The patient had an extremely large liver which post mortem was found to be cirrhotic and to contain a large amount of the pigment found in cases of hemochromatosis. During the day, when the work of the liver was increased because of the absorption of food products, it might be imagined that the liver would be less able to cope with the urobilin brought to it, and the great increase during the daytime might be thus explained. But the wide and irregular fluctuations from day to day and from hour to hour, in spite of the fact that the meals were taken at regular intervals, remain to be accounted for. Possibly some other factor such as a formation of urobilin in the diseased liver may have played a part. In Saillet's two curves of hourly urobilin excretion in people in health, no such wide variations are to be seen.

Other possible factors which may play a part in alterations of the urinary excretion of urobilin are the changes which urobilin undergoes in the blood and tissues. The form in which urobilin circulates in the blood-stream is still unknown, and the question as to whether it may not there in part be broken up or synthesized to some other substance, or may not be stored in some form or other in the tissues, is still unsolved, and it is possible that in them an explanation may be found for these anomalies of urobilin excretion. At present, they can only be recorded.

VI. THE EXCRETION OF UROBILIN IN THE STOOLS

In ten adults in whom there was no reason to suspect any disturbance of hemoglobin metabolism, the average daily excretion in the stools was worked out. These cases, as shown in Table 4, showed variations between 3,307 and 8,737, and a general average of 6,475.

TABLE 4.—Average Daily Excretion of Urobilin in Stools of Ten Adults with Normal Hemoglobin Metabolism

Length of Period of Observation, Days	Diagnosis	Average Daily Urobilin in Stools
8	Inguinal hernia	8,685
15	Fractured femur	3,855
3	Chronic appendicitis	6,080
3	Endometritis	3,307
6	Neurasthenia	4,887
10	Neuritis	8.702
15	Chronic arthritis	6.604
11	Neurasthenia	8,737
6	Fractured femur	5,840
6	Fractured tibia	8,053

The impossibility of gaining any idea as to the amount of urobilin excreted in the stools by an examination of a single twenty-four-hour collection is apparent when the figures for the daily excretion of any of the cases we have worked with are examined (Table 5). The variations, it is seen, are sometimes very large indeed.

To a certain extent, of course, this is accounted for by differences in the quantity of feces passed from day to day, but there are certainly other factors involved. We were particularly struck with the fact that on the days following a period of twenty-four hours during which no stool was passed, there was not as a rule any increase in the urobilin. If the urobilin in the stools retained in the large intestine were absorbed by the blood-stream, one would have expected an increase in the urobilin in the urine on these days. But on reviewing the figures, no constant increase in the urobilin in the urine could be established. We were then inclined to attribute this apparent loss of urobilin to destruction within the intestine; but when the effect of keeping stools in an incubator at 37 C. was tried, we found to our surprise that there was no less marked loss of urobilin.

TABLE 5.—UROBILIN EXCRETED IN STOOL

Day	Urobilin in Stool			
1	2,408	4,800	16,640	5,120
2	10,880	3,360	5,280	13,440
3	*	3,840	7,680	2,560
4	7,360	960	1,440	*
5	4,480	*	4,800	3,840
6	1,280	6,080	15,360	14,400
7	7,680	10,240	25,920	*
8	4,000	8,000	8,320	35,200
9	*	*	3,840	1,536
10	720	3,200	5,760	3,200
11	7,040	11,200	6,720	7,040

* No stool.

The stools were thoroughly ground up in water and kept in the incubator. Every day, 25 c.c. were removed and extracted with acid alcohol. With the exception of the last stool, the figures show only such differences as lie within the limits of error of the method (Table 6). There was only a slight diminution of urobilinogen and increase of urobilin.[3]

TABLE 6.—EFFECT ON UROBILIN OF KEEPING STOOLS IN INCUBATOR

No.	Fresh Stool	After 24 Hours	After 48 Hours	After 72 Hours	After 96 Hours
1	15	16	16	..	..
2	3	3	2	3	3
3	12	19	14	18	11
4	57	62	65	66	65
5	20	21	20	18	24
6	60	55	48	53	60
7	3	3	3	4	4
8	65	60	55	51	48

So long then as stools are kept from exposure to light there does not seem to be a very rapid loss of urobilin. Nor, on the other hand, is there any increase such as might have occurred if the formation of urobilin in the freshly passed stool had been incomplete.

The absence of great destruction of urobilin in stools kept under these conditions outside the body does not, of course, preclude the possibility of such an action taking place within the bowel, where absorption and excretion are proceeding and where there is no exposure to air. It was thought that an indication of such a loss of urobilin either by absorption or destruction was obtained when the relative amounts of urobilin present in the contents at different levels of the intestinal tract were compared.

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[3] Later experiments showed that there was a gradual diminution of both urobilin and urobilinogen, so that after a week about a quarter of the original dilution value had been lost. The greater constancy in the experiment given here was due to concentration by evaporation.

The feces obtained at post-mortem in five cases were ground up in so much acid alcohol as gave, so far as could be seen, an approximately equal consistency. The relative amounts of urobilin were as follows: duodenum, 1; jejunum, 1.2; ileum, 4.8; cecum, 12.3; descending colon, 5.5.

The relative decrease in the descending colon as compared with the cecum certainly suggests a loss of urobilin, but the number of cases examined was too small to permit of any definite conclusion. In all probability, both absorption and destruction are at work. The absence of increased urobilin in the urine on the days of constipation is not by any means conclusive evidence against the occurrence of absorption of urobilin from retained stools, for the absolute want of any relationship between the amount of urobilin in the stools and in the urine is a fact which must impress any one who makes such concomitant observations. No doubt the quantity in the intestine is a factor in determining the amount excreted by the urine, but except under conditions such as an unusually large hemoglobin destruction, when there may be a very great increase of urobilin in the stools, its effect is altogether overshadowed by other influences at work on the urobilin in its passage through the blood-stream, liver, bile, tissues and kidneys.

The interpretation of the results of urobilin estimations in the stools is a comparatively simple matter when compared with the complexities and obscurities surrounding the question of the elimination of urobilin in the urine, and we believe that from a clinical point of view, work on the stools will give results of much greater value and of much less doubtful significance than has been the case up to the present, when the attention of clinicians has been directed almost exclusively to the urine.

Our own experience in cases of pernicious anemia, and the reports of Simpson in cases of malaria have convinced us that, if constipation or diarrhea are avoided, the determination of the average stool urobilin over a period of several days is the best guide we have to the quantity of hemoglobin which is being broken down in the body. Its importance in anemias and in all cases in which excessive blood destruction is suspected does not need to be elaborated.

VII. THE EXCRETION OF UROBILIN IN BILE

Urobilin has been found in human bile post mortem by Jaffé, Müller, Tissier, Gerhardt, Beck and Braunstein. After the introduction of Ehrlich's reagent, urobilinogen was found in forty-three of forty-six cases by Kimura. Neither is constantly present, for in cases in which severe diarrhea had occurred, or in which there had been obstruction to the flow of bile into the intestine, they were not found. Austin and Ordway in a very careful study found urobilin present in 94 per cent. of fifty cases with biliary fistulas in which urobilin was present in the stools and urine. In seven cases in which no urobilin could be demonstrated in either the stool or urine, urobilin was present in the bile in two. Fischler found urobilin in the bile of normal dogs. After establishing a biliary fistula and obstructing the common bile-duct, urobilin disappeared from the bile, but it was still found, though in diminished amount, in the stools. When the liver was damaged by amyl alcohol, urobilin appeared in considerable amounts in the bile. He believes that the only way in which this can be accounted for is by assuming that the urobilin was formed in the liver itself.

Our experience with bile removed post mortem goes to show that the amount of urobilin is extremely variable. In Table 7 the value of the urobilin in 10 c.c. of bile is given in sixteen cases.

TABLE 7.—UROBILIN IN BILE REMOVED POST MORTEM

		Dilution Value in 10 c.c. Bile
1.	Pernicious anemia	3,940
2.	Pernicious anemia	80
3.	Pneumococcal meningitis	2,100
4.	Pyonephrosis	4,500
5.	Bronchopneumonia	650
6.	Streptodiplococcal septicemia	0
7.	Cerebral embolism	620
8.	Aneurysm	300
9.	Aortic incompetence	45
10.	Diabetes	200
11.	Bronzed diabetes	1,800
12.	Carcinoma of liver (without duct obstruction)	45
13.	Tetanus	0
14.	Carcinoma of larynx	0
15.	Hypophysis tumor	0
16.	Adherent pericarditis and valvular disease	0

Of these sixteen cases there were five in which no urobilin was found by the method we used. But if larger amounts of bile had been used for extraction we might have found traces, and we therefore cannot say more than that the quantity was at least very small. No relation was found between the length of time between death and examination of the bile and the amount of urobilin found. In one case urobilin to a dilution value of 1,800 for every 10 c.c. of bile was present, although it was removed from the body within three-quarters of an hour after death. It does not seem that post-mortem decomposition of bilirubin can possibly explain the variations in quantity which were found.

On the other hand, there is no obvious connection between the nature of the disease and the amounts obtained. We are inclined to believe that the degree of absorption of urobilin from the intestine just before death is an important factor. In the two patients with pernicious anemia, estimations of the amount of urobilin present in the intestinal contents were made, and an enormous quantity was found in the case which contained so much urobilin in the bile, and comparatively little in the one which showed a low dilution value. In another case in which severe diarrhea had completely emptied the intestine, no urobilin could be detected in the bile. In a dog which died four days after the common bile-duct had been severed and in whose intestines no urobilin was found. there was also no urobilin in the bile, although it was found in the bile of normal dogs. These observations bear out the well-recognized importance of the intestinal source of biliary urobilin, and yet exceptions are sufficiently striking to make one hesitate to accept the exclusively enterogenous origin of urobilin.

In a few cases with biliary fistulas after operations for gall-stones the urobilin in the bile was found to increase as the bile began again to enter the intestine, but there was no definite qualitative relationship between the amount in the bile and in the stools. An exception was found in one patient whose case is discussed later, in whom urobilin was present in large amount in the bile while urobilin was practically absent from the stools. This was a case of gall-stones in which for a period of eight days after a gall-bladder fistula had been established, the total urobilin in the stools amounted to only 720 dilutions, while in the bile an amount equivalent to 35, 144 dilutions was found. The stools contained no more urobilin than we found in a case in which there was undoubtedly a complete occlusion of the common duct. Probably no bilirubin at all was entering the intestine. Later on when the bile again passed through the common duct, the urobilin increased in amount in the stools to 33,216 dilutions in seven days, but the percentage of urobilin in the bile, which still came from the fistula for the first four days of this period, was only 230 dilutions for each hundred c.c. of bile, in contrast with 1,360 when there was practically no urobilin in the stools. In cases of this sort it is difficult to avoid the conclusion that the urobilin has been formed in the liver itself.

VIII. UROBILIN IN SERUM

Urobilin is present in the intestine and is excreted in part by the kidneys. It presumably reaches the kidneys by means of the blood. One would expect to be able to detect it in the blood of those not infrequent patients in whom even more urobilin is found in the urine than in the stools. Yet there is no point in the whole subject on which there is more diversity of results and of opinions. The constant absence of urobilin from the serum in cases of urobilinuria was a main support of the theory advanced by Gilbert and Herscher that urobilin was formed from bilirubin during excretion through the kidneys. Even long after the inadequacy of this hypothesis had been exposed by the work of Müller and the intestinal origin of the urobilin of the urine had been generally accepted, no one was able to demonstrate the presence of urobilin in the blood or serum. Müller and Gerhardt believed that it was not present in appreciable amount in the blood, and Schlesinger reported fifteen cases of very marked urobilinuria in which the serums gave a negative reaction for urobilin.

It was not until 1906 that Huber published a report in which he stated that urobilin was always found in serum when urobilin was present in the urine. He ascribed the negative results of Schlesinger to the fact that he had not added Lugol's solution to the zinc acetate filtrate in order that urobilinogen might be oxidized to urobilin. But considerable doubt was cast on Huber's results when it was pointed out that the green fluorescence characteristic of urobilin might be closely imitated by biliverdin, and that especially after the addition of Lugol's solution, the bilirubin normally present in serum might be oxidized to beliverdin. Biffi (1907) extracted oxalated blood with chloroform, examined the filtrate spectroscopically and found urobilin present in small quantities in a number of cases and stated that in lobar pneumonia it was almost constantly found. Moller could not confirm Biffi's findings as to the relative frequency of a positive reaction for urobilin in serum, but with zinc acetate and Lugol's solution found it in only two cases, both lobar pneumonias, and later with Biffi's method in two other cases, pneumonia and one of pernicious anemia.

Further evidence of the occurrence of urobilin in serum was given by von Jaksch, who stated that in fatal cases of pneumonia the serum separated from blood removed by venesection showed a green fluorescence which disappeared on exposure to light. Conner and Roper (1909), in a study of the relation between the bilirubin in serum and urobilin in the urine, repeatedly and carefully examined the serums of over sixty patients with urobilinuria, with uniformly negative results, until the serum of a patient dying of lobar pneumonia was encountered. This serum gave a markedly positive reaction for urobilin with all the methods. In nine other cases of pneumonia shortly before death the serum contained large amounts of urobilin. In three severe cases of pneumonia in which the patients recovered, urobilin was detected in small amount in the serum, but in fifteen other cases in which the patients lived, no urobilin was found. There was no parallelism between the amount of urobilin in the serum and in the urine.

Lehndorf (1913) could find urobilin in only two of the serums which he investigated. One was from a case of decompensated mitral stenosis and the other from a case of myocardial degeneration with pleurisy shortly before death. Fromholdt and Nersessoff (1912) by a somewhat complicated method and by extracting relatively large volumes of oxalated plasma, were able to demonstrate urobilin in the serum of seven out of eleven cases with urobilin in the urine. They record a doubtfully positive reaction in a case of occlusion of the common duct with no urobilin in either the stools or the urine. The spectroscopic band of urobilin became unmistakable after the addition of iodin, but they are inclined to think that this may possibly have been due to a conversion of bilirubin into urobilin.

Hildebrant (1909), who, after many negative results, found the spectrum of urobilin in the serum in a case of pneumonia shortly before death, believes that urobilin normally circulates in the blood as urobilinogen, because in this case the urobilin band appeared only after the serum had been exposed for some time to light and air. He obtained a red color on mixing Ehrlich's reagent with the serum before the urobilin had appeared. Moller, though he is inclined to agree with Hildebrandt, points out the technical difficulties of urobilinogen recognition in serum, since the hydrochloric acid precipitates the proteins. He obtained an apparently positive reaction in only two of his cases. In three cases Conner and Roper showed the characteristic red color and confirmed the presence of urobilinogen by finding the absorption band of the benzaldehyd compound. But in the other cases in which urobilin was present they did not find any urobilinogen.

Conner and Roper's spectroscopic recognition of urobilinogen is the only observation which can be taken as approaching to a proof of the presence of this body in serum, and in view of the substances of the indol group which may give a spectrum very similar to that of the urobilinogen compound, their statement cannot, in the absence of any data as to the position of the absorption band, be taken as decisive.

In fact, the evidence so far points in just the opposite direction and seems to indicate that urobilin, instead of circulating in the reduction form of urobilinogen, is present as an oxidation product which does not possess the spectroscopic characteristics of urobilin and so escapes detection. This evidence is all the stronger because it has been collected independently by three observers since 1903; none of whom apparently knew about the work of the others. Finding no urobilin in the blood of cases in which he expected it, Schlesinger tried the effect of adding urobilin to serum and to blood. He discovered that whereas it was readily demonstrated in the serum, it disappeared in the whole blood or in serum to which red blood-cells had been added. Clarens made the same observation and in 1911 Roth and Herzfeld confirmed Schlesinger's experiment and suggested that the disappearance of the urobilin might be due to oxidation.

They found that oxygenated serum destroyed the urobilin and that in whole blood its disappearance might be delayed by carbon dioxid. In a few cases, though not in all, they were able to demonstrate the presence of urobilin in serum after it had stood for from twenty-four to forty-eight hours mixed with finely powdered zinc. Since urobilinogen is found in the urine of patients in whom no urobilin can be found in the serum, it seems that the kidneys must possess the faculty of reducing the oxidized urobilin. They were able to carry out only two experiments with kidney extracts, one of which gave a definite production of urobilin in a serum in which it had previously been found absent. It is noteworthy that urobilin was formed with an alcoholic kidney extract, so that the process cannot depend on any vital activity in the cells.

The conception of the oxidation of urobilin in the blood-stream is strengthened when it is remembered that the only cases in which urobilin has been with certainty found in the serum are those in which there was a great reduction in the available oxygen of the blood. They have been almost without exception cases of lobar pneumonia shortly before death.

The effect on urobilin of the blood and tissues opens up a new field for investigation and it is not improbable that along these lines facts may be discovered which will throw light on the present obscurity.

IX. ANIMAL EXPERIMENTS

The Excretion of Urobilin in Animals

No satisfactory estimations could be made on the stools of rabbits or goats because the amount of urobilin was too small.

The same difficulty, though to a lesser extent, was encountered in dealing with the excreta of cats and dogs. Even when the extract was made as concentrated as possible it seldom required more than a few dilutions to obliterate the spectra of urobilinogen and urobilin. We have not been able to find any systematic investigation of the pigments of the stools of dogs or cats, but it is known that cholecyanin,[5] a derivative of bilirubin which is not regularly present in human stools, is constantly found. Possibly the greater part of the bilirubin in the intestine of these animals may be excreted in other forms than urobilin. Certainly the acid alcohol extracts of the stools contained a large amount of light-absorbing material, so much so as to render the urobilin band somewhat obscure at the low dilution at which it had to be read. And not infrequently other absorption bands were seen. The method did not then give such definite and clear results as were obtained with human stools.

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[5] Fischler: Inaug. Diss., Heidelberg, 1906, p. 84.

It was soon found that such small amounts of urobilin as were detected varied considerably from day to day. No satisfactory explanation for this variation was obvious, but one possible factor appeared to be the length of time during which the feces remained in the intestine. Hard constipated stools as a rule contained very little urobilin. The following experiment shows how markedly the quantity of urobilin increases during regular action of the bowels as compared with a period of constipation.

Dogs B, C and D were normal. Dog A had had a biliary fistula and a closure of the common bile-duct. At the time of this experiment the fistula was closed and the common duct was again patent. Urobilin was present in the urine and was added to the amount in the stools. The figures (Table 8) represent the total dilution value of the urobilin excreted during ten days. In the first period the dogs were constipated; in the second sufficient cascara was given to obtain a stool every day without giving rise to marked diarrhea.

TABLE 8.—Urobilin in Constipation and in Regular Bowel Action

	First Period of Ten Days		Second Period of Ten Days	
	Urobilin	Number of Stools	Urobilin	Number of Stools
Dog A	5,640	4	13,120	10
Dog B	14,400	8	19.200	10
Dog C	9,200	5	16,420	10
Dog D	12.860	7	37.200	9

In these four dogs the total urobilin during the period of constipation was 42,100 and in the period during which cascara was given, 85,940, more than twice as much. During another ten-day period castor oil was given, and the total amount passed was 51,250, but regular daily movements were not obtained. Constipation, therefore, in dogs diminishes the amount of urobilin in the stools. We are satisfied that this is true for man also though we cannot bring forward any systematic evidence. The diminution may be due either to increased absorption of urobilin from the intestine or to destruction of the urobilin. If increased absorption were the cause, the excretion of urobilin in the urine should be increased. In normal dogs or cats urobilin was never found in the urine in sufficient amount to estimate. But in Dog A, in which the common duct had been tied and a biliary fistula made, it was found six months later that communication between the bile-ducts and the intestine had become reestablished and that the fistula had closed. In this animal considerable amounts of urobilin were constantly present in the urine. The cause of this was found at death to be an extremely marked cirrhosis of the liver, which had developed probably as a result of infection through the fistula combined with the initial bile stasis.

TABLE 9.—UROBILIN IN URINE AND IN STOOL OF DOG A

Date	Urobilin in Urine	Urobilin in Stool
Dec. 2	160	No stool
Dec. 3	248	800
Dec. 4	192	800
Dec. 5	224	No stool
Dec. 6	21	400
Dec. 7	100	No stool
Dec. 8	160	No stool
Dec. 9	120	No stool
Dec. 10	240	No stool
Dec. 11	400	1,200
Dec. 12	520	No stool
Dec. 13	240	No stool
Dec. 14	280	800
Dec. 15	80	No stool
Dec. 16	200	800
Dec. 17	600	No stool
Dec. 18	160	No stool
Dec. 19	680	400
Dec. 20	480	No stool
Dec. 21	500	No stool

Increased absorption during constipation might be expected to show itself in a rise of urobilin in the urine in this case. Yet we were not able to establish any such increase in urinary excretion. The average amount of urobilin in the urine on the seven days in which urobilin was lost from the body in the stools was 273, and 272 on the thirteen days during which urobilin was retained in the intestine. This evidence would have been more convincing if we had succeeded in contrasting a period of regular evacuation with a period of constipation, but on giving cascara it was found to be impossible to be sure of excluding contamination of the urine with the stools. Still if the figures for the four days from December 3 to December 6, inclusive, during which three stools were passed, are contrasted with those from the 7th to the 10th when there were none, it is seen that a total of 685 dilutions of urobilin were present in the first period, and only 620 when the bowels did not act at all.

It seems probable, therefore, that destruction of urobilin plays a much larger part than increased absorption in the diminution of urobilin which occurs during constipation. This is only what would be expected of a substance which outside the body is so readily altered.

Diarrhea, unless it is so pronounced as to lead to the excretion of unaltered bile, does not seem to have nearly so great an influence in diminishing the quantity of urobilin.

The total excretion of urobilin per kilogram of body-weight in dogs which had been kept under exactly the same conditions and on the same diet for a long time was determined over a period of forty-one days (Table 10).

TABLE 10.—EXCRETION OF UROBILIN PER KILOGRAM OF BODY-WEIGHT

	Weight, Kg.	Dilution Value Per Kg.
Dog C	7.82	6.100
Dog B	9.95	5.220
Dog D	17.80	5.450

Dog A, with cirrhosis of the liver, which was also kept under the same conditions for the same time, and which during that period exhibited no obvious signs of ill health, weighed 4.02 kg. and excreted urobilin with a dilution value of 8,806 per kilogram body-weight. This is an increase of 58 per cent. over the average excretion of urobilin in the three normal dogs. It does not seem probable that an increased hemoglobin metabolism could account for this. It appears much more likely that there was either a diminished destruction of urobilin or an increased formation of urobilin from bilirubin. Constipation was present to a more marked degree in this dog than in the others, so that the increase of urobilin was probably even more marked than the figures suggest. A diminished destruction, if such occurred, must have operated in the body itself. If one of the functions of the liver is the synthesis of urobilin absorbed from the intestine into bilirubin, an explanation of the increase in urobilin excretion is afforded by the supposition that the diseased liver in this case allowed much of the absorbed urobilin to pass through it into the general circulation to be excreted in the urine. But the possibility of the increase in urobilin being due to a formation of urobilin from bilirubin in the diseased liver cannot be excluded. Outside the body we found that urobilinogen and urobilin were produced in considerable amounts in bile left at a temperature of 37 C. And it seems possible that such a breaking down of bilirubin may occur in stagnating bile especially if an infection of the bile passages exists.

In attempting to follow the effect of closure of the common bile-duct in dogs on the urobilin excretion, a difficulty was encountered in connection with the methods we used. In the alcoholic stool extracts a pink color was produced which apparently showed the spectroscopic absorption of urobilinogen. That in reality it was some other substance was shown by the difference in the color reaction with Ehrlich's solution and also by the fact that on exposure to light of the zinc acetate filtrate the absorption band still persisted instead of disappearing. In all probability this substance was indol or some derivation of indol. Von Moracewski found that in alcoholic stools there is an increase in indol which has an absorption band very similar to that of urobilinogen.

To avoid confusion with this substance we have taken no account of the urobilinogen either before or after the closure of the common bile-duct. This makes the total amounts given inaccurate, but our object was to see whether or not the absence of bile from the intestine would completely stop all excretion of urobilin. As is seen from the two experiments reported below, urobilin disappears for a time, but it afterward returns in diminished though relatively not inconsiderable amount in the stools. In both these cases also urobilin after an interval was found in the urine. The impossibility of obtaining urobilin-free stools in dogs even though all bile is prevented from entering the intestine has been noted by Fischler. Brugsch and Yoshimoto found that urobilin reappeared after an interval in the stools of a dog with biliary fistula.

OBSTRUCTION OF COMMON DUCT

Dog E.—Section of Common Duct Removed

Icterus, acholic stools and bile in the urine appeared. At the post-mortem a distended gall-bladder and ducts were found. No communication with the intestines. A few patches of organized lymph were found on the liver and adhesions round the resected duct but no general peritonitis. Urobilin given as total amounts in periods of six days. (Table 11.)

TABLE 11.—Total Urobilin, Dog E, in Periods of Six Days

Period	Stools	Urine
BEFORE COMMON DUCT CLOSURE		
First	3,200	0
Second	2,320	0
AFTER COMMON DUCT CLOSURE		
Third	0	0
Fourth	512	185
Fifth	32	56
Sixth	320	0
Seventh	160	76

Dog F.—Section of Common Bile-Duct Removed

Uninterrupted recovery with development of jaundice. At the post-mortem the gall-bladder and ducts were found to be greatly distended. There was no communication between them and the intestine. The urobilin is given as a total of estimated dilution value for the stools and urine passed in periods of six days. (Table 12.)

TABLE 12.—Total Estimated Dilution Value of Urobilin, Dog F, in Periods of Six Days

Period	Stools	Urine
BEFORE COMMON DUCT CLOSURE		
First	9,312	0
Second	5,120	0
AFTER COMMON DUCT CLOSURE		
Third	0	0
Fourth	0	0
Fifth	576	396
Sixth	2,368	1,084

BILIARY FISTULA WITH OBSTRUCTION OF COMMON DUCT

In three other dogs the common duct was obstructed and a biliary fistula established. No jaundice developed.

Here also the amount of urobilin in the stools decreased, but did not disappear. Urobilin appeared in the urine of Dog A, which was afterward found to have developed a cirrhosis of the liver. In the other two it was absent. The urobilin is given as the total dilution values of six-day periods. (Table 13.)

After death no communication was found between the bile-passages and the intestine in Dogs G and H.

TABLE 13.—Total Dilution Values of Urobilin, Dogs G, H and A, in Periods of Six Days

Period	Stools	Urine*
BEFORE OPERATION		
Dog G: First	1,920	0
Second	1,590	0
Third	3,524	0
AFTER OPERATION		
Fourth	240	0
Fifth	1,845	0
Sixth	560	0
Seventh	384	0
BEFORE OPERATION		
Dog H: First	1,744	0
Second	930	0
Third	632	0
AFTER OPERATION		
Fourth	64	0
Fifth	176	0
Sixth	688	0
BEFORE OPERATION		
Dog A: First	3,480	0
Second	3,256	0
AFTER OPERATION		
Third	728	0
Fourth	520	22
Fifth	280	68
Sixth	1,260	26
Seventh	632	239
Eighth	720	...

* Urobilin was occasionally found in the urine, but this was due to contamination with bile. It was at first difficult to prevent the urine wetting the dressings and taking up some of the bile which was rich in urobilin.

The presence of urobilin in the stools after closure of the common bile-duct cannot be explained as due to the excretion of bilirubin into the intestine from the blood, for it was also found in the stools of the dogs in which the bile was allowed to drain out of the body and in which there was no increase of bilirubin in the blood. The only possible explanation seems to be that urobilin itself was excreted from the blood into the intestine. Where was this urobilin produced? Urobilin is known to have formed in old hematomas in various parts of the body, so that the formation of urobilin from bilirubin in the tissues of the icteric dogs is a possibility. But the fact that it also was found in the excreta of dogs which were not jaundiced points to the liver as the place of formation, for in the dogs with biliary fistula this was the only organ in which bile was present. Urobilin was found in the bile escaping from the fistulas.

We must conclude then that in dogs the intestine is not the only site of origin of urobilin, but that under certain conditions urobilin is formed in the liver. Whether or not this is a normal function of the liver is another question which will be discussed later.

These experiments, though few in number and inconclusive in their results, are yet sufficient to show the complexity of the subject and the number of factors which may play a part in excretion of urobilin. Variations in the amount of formation of urobilin in the intestine or in destruction after it has been formed, the degree of absorption from the intestine, the fate of the absorbed urobilin in the liver, whether it is rebuilt to bilirubin or is allowed to pass into the general circulation, the question as to a change of bilirubin into urobilin in the liver under certain conditions, and the possibility of the excretion of urobilin from the blood into the intestine are some of the points which have to be considered in interpreting the results.

In any case we must conclude that in dogs at least the theory of the exclusively enterogenous origin of urobilin does not suffice to meet the facts.

X. CLINICAL REPORTS

To enumerate all of the conditions in which urobilin has been found in excess clinically does not seem to us desirable as we wish to point out the significance of its occurrence in the few in which its clinical study has been found to be of most value. The following clinical reports are selected from a series of observations made by us during the last two years.

Diseases of the Liver without Much, if Any, Interference with the Entrance of Bile into the Intestine

TABLE 14.—SUMMARY OF CASES 1-6

No.	Case	Length of Period of Observation, Days	Diagnosis	Average Daily Urobilin	
				Urine	Stools
1	I. N.	53	Portal cirrhosis	572	3,647
2	A. F.	10	Portal cirrhosis	241	3,088
3	C. D.	14	Cirrhosis (syphilitic)	456	3.451
4	C. B.	30	Bronzed diabetes	5,800	7,400
5	F. M.	4	Hanot's cirrhosis	2,034	3,360
6	F. O'B.	15	Abscess of the liver	1,713	4,047

CASE 1.—I. N., enlarged liver with ascites. Red blood-cells about 3,000,000 and hemoglobin 55 per cent. Remained during the time of observation in about the same condition. Fluid was removed from the abdomen on several occasions. Urobilin was never found in it. There was a slight grade of jaundice, the serum on one occasion showing six times the normal amount of bilirubin. One month after the estimations were discontinued the patient died and the liver showed a well-marked portal cirrhosis. Chart 8 shows the urinary and stool excretion

of urobilin. The stools were given as averages for periods of three days to diminish variations due only to changes in the motor activity of the colon and rectum. The considerable variations in the quantities in the stools and the fact that urobilin was not constantly found in the urine are the noteworthy points in this case.

Case 2.—A. F. A typical case of portal cirrohosis.

Case 3.—C. D. Small liver, large spleen, hematemesis melena. Glycosuria with polyphagia, polydipsia and emaciation. Positive Wassermann.

Case 4.—C. B. Very much enlarged liver and spleen. Ascites. Pigmented skin. Glycosuria. At post-mertem the diagnosis of bronzed diabetes was confirmed by the finding of a deeply pigmented cirrhotic liver and pancreas. Chart 9 shows the great variations in the amounts of urobilin in the urine.

Case 5.—F. M., A man aged 48 complaining of persistent slight jaundice of two years' duration. No loss of weight. No pain. General health good. Liver greatly enlarged, extends 10 cm. below costal margin. Spleen much enlarged, projects 12 cm. below costal margin. No ascites. Urine contains bile. Red blood-cells 4,400,000. Hemoglobin 86 per cent. Negative Wassermann.

TABLE 15.—Daily Urobilin in Case 5

Date	Urine	Stools
November 23	1,300	4,800
November 24	2,950	5,120
November 25	1,104	960
November 26	2,784	2,560

Case 6.—F. O'B. Admitted with a temperature and polymorphonuclear leukocytosis, complaining of pain and tenderness in the right hypochondriac region. On the eighth day after admission the abdomen was opened and a large abscess of the liver drained.

In this group of cases the urobilinuria is evidently not due to an increased formation of urobilin in the intestine, for the quantities found in the stools are not above the normal limits. There is no evidence of any overflooding of the liver by urobilin derived from an increased destruction of hemoglobin. That the abnormal quantity of urobilin in the urine is to be ascribed to the pathological changes in the liver which were present to a marked degree in all these cases is suggested not only by the constancy of the association of urobilinuria with liver disease which has been noted by all observers, but also by the fact that in particular cases it is possible to observe the diminution and final disappearance of urobilin from the urine in those cases in which an abnormal condition in the liver is removed. The case of F. O'B. with a large liver abscess was a good example of this. During the week preceding the opening of the abscess the average daily excretion was 2,187. For a few days after the operation the quantity in the urine remained high and then dropped so that the daily average for the seven days after operation was only 244.

It will be noted that it is not possible to exclude pronounced disease of the liver by a failure to find urobilin in the urine on one examination. As may be seen from the chart of the case of I. N. (Chart 8, Case 1), who had a very marked cirrhosis of the liver, there was a period of five days during which no urobilin could be detected. And even in the

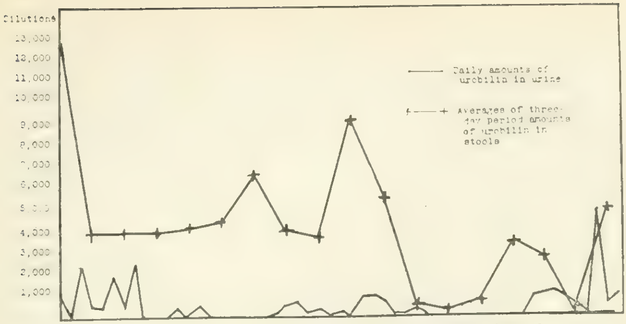


Chart 8.—Urinary and stool excretion of urobilin, Case 1.

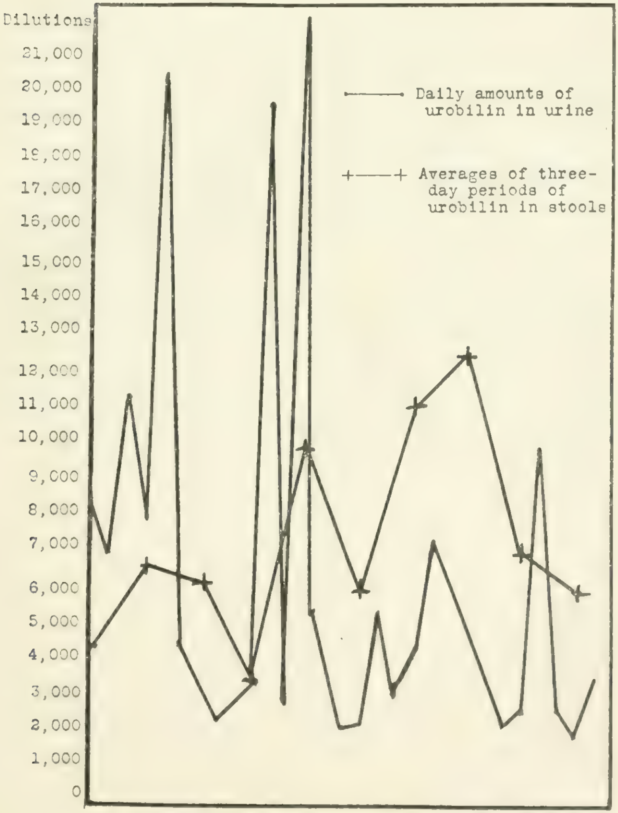


Chart 9.—Urinary and stool excretion of urobilin, Case 4.

patient C. B., in whose urine there was as a rule such a large amount of urobilin, none was found in one twenty-four-hour specimen. The fluctuation in the quantity of urobilin from hour to hour and from day to day makes it imperative to take the average of a series of twenty-four-hour specimens before an idea can be obtained as to the grade of urobilinuria in any particular case.

The study of a large series of cases of liver disease along these lines, with concomitant estimations of the urobilin in the stools and in association with other tests of hepatic efficiency, will be necessary before it is possible to say whether or not the degree of urobilinuria may be taken as an approximate guide to the amount of impairment of liver function.

Cases in Which Part of the Bile Entered the Intestine and Part Left the Body through a Gall-Bladder Fistula

TABLE 16.—Summary of Cases 7 and 8

No.	Case	Length of Period of Observation, Days	Diagnosis	Average Daily Urobilin Bile	Average Daily Urobilin Urine	Average Daily Urobilin Stools
7	A. R.	18	Cholelithiasis	788	0	4,240
8	B. H.	13	Chronic cholecystitis	1,505	0	2,669

Case 7.—A. R. This patient was operated on for relief of dyspeptic symptoms. No icterus. A thickened gall-bladder containing a large stone was found. The gall-bladder was drained. There was no jaundice following the operation.

Case 8.—B. H. Operated on for symptoms of dyspepsia. No jaundice before or after operation. A moderately thickened injected gall-bladder with adhesions was found and drained.

In these cases there was no obstruction to the flow of bile through the common duct, and only a part of the bile escaped from the fistula.

The urobilin found in this fraction of the bile is of interest in connection with the question as to how much of the urobilin is simply excreted again into the intestine after absorption by the portal blood-vessels. To judge from these two cases, it would appear that a very large part of the absorbed urobilin is excreted into the intestine unchanged. But it must be remembered that neither of these was a normal case, and that the possibility of the formation of urobilin in the liver itself existed.

Complete Obstruction to the Entrance of Bile into the Intestine

TABLE 17.—Summary of Cases 9-12

No.	Case	Length of Period of Observation, Days	Diagnosis	Average Daily Urobilin Urine	Average Daily Urobilin Stools
9	F. W.*	34	Carcinoma of hepatic ducts	0	178
10	G. W.	5	Carcinoma of stomach	0	0
11	A. M.	6	Carcinoma of pancreas	0	0
12	B. M.	3	Carcinoma of duodenum	0	0

* Thirty-five gm. of dried bile were given to this patient by mouth in an attempt to confirm Müller's experiment in which he succeeded in producing urobilinuria in such cases. No urobilin appeared in the urine, but this may have been due to the form in which the bile was given. Fromholdt also obtained negative results with various preparations of bile and found that it was necessary to give fresh bile as Müller himself did. Some of the urobilin found may have been derived from bile given by mouth, but it was also found before it was taken and also more than two weeks afterward.

Case 9.—F. W. This was a case which we have already reported in which there was a large liver, deep jaundice and clay-colored stools. At the post-mortem a large carcinomatous mass in the liver was found to have completely obstructed the hepatic duct.

Case 10.—G. W. Jaundice had been present for two weeks before the estimations were made. Afterward, at operation a pyloric carcinoma obstructing the common duct was found.

Case 11.—A. M. Deep jaundice of several months' duration. Post mortem a scirrhous carcinoma of the pancreas was found.

Case 12.—B. M. At operation, a carcinoma of the duodenum was found which completely obstructed the ampulla of Vater.

In these four cases, no bile was entering the intestine except such traces as might be excreted from the blood. Bile was present in all the tissues of the body, and practically the only mode of excretion was through the urine.

The law of the enterogenous theory of the origin of urobilin, that without the entrance of bile into the intestine, no urobilin is formed, is borne out by the last three cases but not by the first.

In itself, we should not have been inclined to attribute much importance to this exception, if it had not been that Fischler and we ourselves had found urobilin in the stools of dogs with closed common ducts, and that several observers (Gerhardt, Hoppe-Seyler, Tsuchuya and Fischer and Meyer-Betz) have even found urobilin in the urine when no bile was entering the intestine.

Our method gives positive results in the urine only when the amount is distinctly larger than normal, so that urobilin may very well have been present. And it is noteworthy that we found urobilin in the fluid removed post mortem from the broken-down cancer tissue in the liver.

In the other three patients in whom no urobilin could be detected in the stools, the liver itself was not directly involved. It seems, then, that this case gives some evidence in support of the hypothesis that the diseased liver may itself form urobilin.

Cases in Which there was Obstruction to the Entrance of Bile into the Intestine and in Which Part of the Bile Left the Body through a Gall-Bladder Fistula

TABLE 18.—Summary of Cases 13 and 14

No.	Case	Length of Period of Observation, Days	Diagnosis	Average Daily Urobilin Bile	Urine	Stools
13	A. R.	5	Cholelithiasis	0	0	0
14	E. W.	8	Cholelithiasis	5,856	640	160

Case 13.—A. R. Admitted with typical signs of acute cholecystitis. Slight icterus but no bile in the urine. The gall-bladder was drained. For the first few days the jaundice deepened and bile appeared in the urine. Thereafter, it diminished and on the fifth day after operation the urine was free from bile. On the seventh day no icterus could be detected.

CASE 14.—E. W. The patient was operated on for symptoms of gall-stones. There was no jaundice. A stone was removed from the common duct and the gall-bladder drained. After the operation there was deep jaundice, acholic stools and bile in the urine.

In both of these patients the manipulations during the operation caused a closure of the common duct, and the drainage through the fistula was not sufficiently free to prevent the occurrence of jaundice. There was, therefore, a complete or almost complete obstruction to the passage of bile into the duodenum combined with the escape of a part of the bile through the gall-bladder fistula.

Though clinically so similar, there is, nevertheless, a remarkable contrast in the urobilin figures. The patient A. R. might be cited as an excellent example in support of the purely enterogenous origin of urobilin, while the patient E. W. appears to offer very strong evidence in support of the possibility of the formation of urobilin in the liver under certain conditions.

The subsequent course of urobilin excretion in these two cases appears to be worthy of mention, and for this purpose it is most conveniently divided into periods corresponding with changes in the biliary excretion.

In Case 13, during the days immediately following the operation, when bile was still present in the intestinal tract, considerable amounts of urobilin were found in the urine and some in the bile. (Table 19, first period.) Thereafter, during the time in which there was jaundice, acholic stools and bile in the urine, urine, no urobilin was found either in the bile or urine. (Table 19, second period.)

In the third period, the jaundice diminished, the stools became colored, and with this urobilin reappeared in the bile and urine.

The fourth period seemed to illustrate the effect of recovery of the liver function, for as the patient's condition improved, the urobilin was found to diminish and at last disappear from the urine in spite of the fact that more bile was entering the intestine because of the removel of the gall-bladder drain.

TABLE 19.—UROBILIN IN CASE 13

Period and Date	Bile	Urine	Stools
First	432	1,270	*
Second	0	0	0
Third	492	1,240	5,896
Fourth:—			
April 1	144	704	0
April 2	18	864	1,600
April 3	†	656	7,680
April 4	...	448	8,960
April 5	...	0	7,680
April 6	...	0	6,400
Fifth:—			
May 1	0	0	160
May 2	0	1,224	240
May 3	0	3,900	64
May 4	84	4,480	‡
May 5	36	7,800	19,540
May 6	120	5,040	6,784
May 7	224	1,700	9,230

* No stools.
† Drain removed.
‡ Stool lost.

Three weeks later the patient returned with recurrence of the cholecystitis and at least a partial blocking of the common duct. On May 1 the fistula was reopened and much bile, mucus and pus escaped. Urobilin, present at first in very small amounts in the stools, increased in the next few days and urobilin reappeared in the urine and bile. (Table 19, fifth period.) During the whole of the next month during which the patient was under observation, urobilin was present in considerable amount in the urine, as if during this second attack, the liver had suffered some more lasting damage. Subsequently, though sometimes found in small amounts, it was often absent.

This case, therefore, supports what may be called the orthodox theory of the necessity of the presence of bile in the intestine for the production of urobilin, and also may be taken as illustrating the effect of damage to the liver on the urinary excretion of urobilin.

On the other hand, Case 14 cannot be reconciled with the exclusively enterogenous origin of urobilin and is the clearest instance we have encountered of the necessity of admitting that, at any rate in some cases, urobilin may be produced elsewhere than in the intestine.

During a time when the stools were colorless, the skin jaundiced, and the urine laden with bile, that is to say when everything pointed to the practical absence of bile from the intestine, there was a very large excretion of urobilin in the bile and a not inconsiderable amount in the urine.

TABLE 20.—UROBILIN IN CASE 14

Period	Bile	Urine	Stools
First	5,856	640	160
Second. (average daily excretion)	1,176	592	3,625

During the next eight days, urobilin reappeared in the stools and the jaundice diminished, but the urobilin in the bile and urine, instead of increasing as one might have expected, decreased in amount.

It seems most probable that in this case the urobilin in the urine during the first period was absorbed by the blood-stream from the urobilin in the bile and excreted through the kidneys. The diminution during the second period, in spite of the reentrance of bile into the intestine, may perhaps be ascribed to a decrease in the formation of urobilin by the liver, as it began to recover its normal functions. In any case, the large amount of urobilin in the bile cannot have been absorbed from the intestines.

If, in such cases as these, a marked urobilinuria may be present in spite of the total or almost total absence of urobilin from the intestine, it would seem to be likely that in all cases of urobilinuria in liver disease, some part at least of the urobilin has an extra-intestinal origin.

CASE 15.—A. H. Pernicious anemia. During the period in which estimations were carried out, the red blood-cells varied from 1,300,000 to 1,800,000 and the hemoglobin from 31 to 38 per cent.

CASE 16.—A. T. Pernicious anemia. The red blood-cells numbered 1,000,000 and the hemoglobin was 28 per cent.

Diseases Associated with Changes in Hemoglobin Metabolism

TABLE 21.—SUMMARY OF CASES 15-19

No.	Case	Length of Period of Observation, Days	Diagnosis	Average Daily Urobilin Urine	Average Daily Urobilin Stools
15	A. H.	25	Pernicious anemia	470	24,977
16	A. T.	12	Pernicious anemia	1,058	22,014
17	E. P.	4	Secondary anemia from intestinal hemorrhage	0	2,400
18	L. S.	4	Primary polycythemia	1,849	3,240
19	H. L.	7	Secondary polycythemia from asthma and emphysema	806	10,011

CASE 17.—E. P. For eleven years the patient had had bleeding from the bowel. The stools were sometimes tarry, sometimes contained bright red blood. No cause was found even after the abdomen was opened. At the time of observation the red blood-cells varied from 2,100,000 to 2,550,000 and the hemoglobin from 27 to 29 per cent. Hemorrhage ceased after a Whitehead operation and the patient entirely recovered.

TABLE 22.—UROBILIN IN CASE 17.

Date	Urine	Stools
November 23	0	5,120
November 24	0	*
November 25	0	2,560
November 26	0	1,920

* No stool.

CASE 18.—L. S. Noticed a bluish tinge in her face and hands three years ago. During the time of observation the red cells numbered from six and one-half to seven and one-half millions and the hemoglobin was over 110 per cent. No normoblasts were found. There was no splenic enlargement.

TABLE 23.—UROBILIN IN CASE 18

Date	Urine	Stools
September 5	4,455	800
September 6	1,560	8,960
September 7	1,080	3,200
September 8	360	*

* No stool.

CASE 19.—H. L. Asthma and emphysema since childhood. Marked and constant cyanosis. At the time of observation there were 7,350,000 red blood-cells, and 120 per cent. of hemoglobin. There was no fever and the general health of the patient was as good as it ever had been.

TABLE 24.—UROBILIN IN CASE 19

Date	Urine	Stools
September 2	980	8,000
September 3	2,016	14,080
September 4	0	11,520
September 5	864	8,000
September 6	0	9,600
September 7	900	4,480
September 8	880	14,400

Pernicious Anemia.—The amounts of urobilin in the stools of these two patients on whom a careful study was made are much higher than we have found in any other condition, although in neither of them was there any acute blood crisis during the time of observation. The quantity in the urine was not very great, but in two other patients from whom the stools could not be obtained for examination, very large amounts were found, corresponding to 4,895 and 16,800 dilutions.

That the increase of urobilin in the urine is in the main due to an overburdening of the liver with an excessive amount of urobilin absorbed from the intestinal tract, and not to a primary functional deficiency of the liver, is most probable.

The marked increase of urobilin in the stools is of special interest as evidence of a distinction between those forms of anemia associated with a great increase in hemoglobin metabolism, such as the cases of pernicious anemia we have cited and others, such as the secondary anemias following hemorrhage and carcinoma, in which the low urobilin content of the stools indicates a diminished destruction of hemoglobin.

Secondary Anemia.—It is especially in cases of secondary anemia that combined urobilin estimations in the urine and stools ought to afford interesting and valuable results.

The case of secondary anemia from hemorrhage which is given above affords a striking contrast when compared with the cases of pernicious anemia. Other cases in which secondary anemia was a complication of some other condition such as carcinoma, showed a diminution rather than an increase in total urobilin excretion.

On the other hand, the case of H. D., who had a diplostreptococcal endocarditis, may be cited as an example of an anemia due to increased blood destruction. During the first twenty-six days the average excretion in the stools was 12,841, twice as great as the normal average, and there was a dilution value of 781 in the urine. During the next seventeen days there was a fall in the stool excretion to 7,801 and in the urine to 659, although there was no increase in the percentage of hemoglobin or red blood-cells. The estimation of red blood-cells and hemoglobin can give no adequate guide as to the total turn-over of hemoglobin in the body, but an approximation to this may be obtained by urobilin determinations in the urine and stools. In cases of anemia of unknown origin, the finding of an increased urobilin excretion might be of diagnostic importance in directing attention to the search for some active blood-destroying agent as the cause.

Polycythemia.—The case of primary polycythemia gave unexpected results. The urobilin in the stools was low instead of being increased, and at the same time there was a very considerable amount of urobilin in the urine, although there was no evidence of any liver disturbance. The finding of urobilin in the urine of the patient with secondary polycythemia was also unexpected.

Both these patients were markedly and constantly cyanosed, and when the connection between cyanosis and the presence of urobilin in the serum is recalled, the question rises as to whether, under normal conditions, a part of the urobilin absorbed from the intestine may not escape the liver and be changed in the blood, except under certain conditions, such as a diminution in the percentage of oxygen, when it might be excreted in the urine.

Unfortunately, we have not had an opportunity of following up this point in other cases with cyanosis.

Miscellaneous Cases

In a large number of patients with various disorders, no pathological increase in the urobilin in the urine was found.

In some, however, who showed no evidence of gross anatomical disease of the liver or of great blood destruction, considerable amounts of urobilin were present in the urine. One of these, a case of alcoholism, is of interest.

The patient was 59 years old and had suffered from attacks of acute gout for forty years. There were large urate deposits round the joints. At the time of observation, he was recovering from a prolonged spell of drinking, and was in a condition of great prostration with complete anorexia and vomiting. There was some edema of the legs. There was no liver or splenic enlargement. A few months later he died suddenly, but the cause of death was not ascertained.

Unfortunately, satisfactory collections of the stools could not be made, but the amount of urobilin appeared to be very low. On one day no urobilin could be detected and on two others amounts of 216 and 1,728 were found.

The urine over a period of nine days showed a daily average of 1,292.

In the absence of any indication of gross liver disease, the most probable interpretation of the appearance of the large amounts of urobilin in the urine in this case is to be found in damage to the functional efficiency of the liver by excessive amounts of alcohol.

In a patient with a huge retroperitoneal sarcoma who was cachectic and feverish, the average urobilin excretion in the urine was 1,545 and 11,893 in the stools. A case of carcinoma of the stomach without any metastases in the liver had an amount in the urine corresponding to 794, and 4,576 in the stools.

These cases are more difficult to interpret than two others in which there were very large masses of cancerous tissue in the liver, in both of which urobilin was found in great excess in the urine.

The patient with cardiac decompensation and swollen liver, whom we mentioned in our first paper, had an average of 2,682 in the urine and 8,619 in the stools.

Three cases of effusion of blood into the tissues were examined, but cannot be said to throw any light on the question as to whether or not urobilin in the urine may have its origin in the breaking down of hemoglobin outside the vessels. One was a case of lymphatic leukemia with hemorrhages into the pharynx, gums and orbital cavities. There was no urobilin in the urine and only 2,792 in the stools.

In a case of caseous tuberculous peritonitis with a large amount of blood in the peritoneal cavity there was an average urinary excretion of 1,264, and in a large pulmonary hemorrhage in a case of compensated mitral stenosis there was an average of 415 in the urine and 15,106 in the stools. There are too many other possibilities which might account for the urobilin in the urine in the two cases in which it was present. Cases of complete occlusion of the common duct with large hemorrhages are the only ones by which it is possible to decide this point.

A disturbance of liver function is, of course, a possibility which is difficult to exclude in almost any case, but it does not seem justifiable at present to attribute every case of excessive excretion of urobilin in the urine without increase in the stools to this cause alone.

XI. CONCLUSIONS

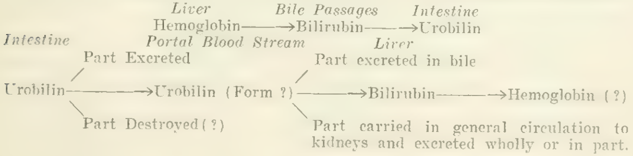
A. General

1. The intestinal formation of urobilin from the decomposition of bile present within the bowel is the usual mode of origin. In complete closure of the common duct due to carcinoma, for instance, there is usually absence of urobilin from the urine, bile and stools.

2. There is evidence that the diseased liver may originate urobilin either directly as a product of its cells, or indirectly from decomposition of bilirubin within the bile passages. Thus, patients in whom no bile is reaching the intestine, may nevertheless show urobilin in large amount in the bile, and to some extent even in the urine and stools if the liver itself is diseased or functionally deficient. The urobilin in the urine and stools of such cases must be due to excretion from the blood of urobilin absorbed from the liver.

The usual sequence in hemoglobin metabolism may be represented as in the accompanying scheme.

SCHEMATIC REPRESENTATION OF USUAL SEQUENCE IN HEMOGLOBIN METABOLISM


Liver
Bile Passages
Intestine
Hemoglobin——→Bilirubin——→Urobilin
Intestine
Portal Blood Stream
Liver
Part Excreted
Part excreted in bile
Urobilin————→Urobilin (Form ?)————→Bilirubin————→Hemoglobin (?)
Part Destroyed (?)
Part carried in general circulation to kidneys and excreted wholly or in part.

On this hypothesis, bilirubin is broken down to urobilin in the intestine and the absorbed urobilin is synthesized in the liver to bilirubin and perhaps by a reverse action again to hemoglobin.

Under abnormal conditions in the liver, formation of bilirubin from the absorbed urobilin from the intestine may fail, and further there may be a reduction of bilirubin to urobilin in the liver itself, a reversal of the normal process.

Under these circumstances, the accumulated urobilin in the liver will be absorbed by the blood-stream and excreted in the urine.

3. An increased quantity of urobilin in the stools indicates increased blood destruction.

In such cases, urobilin may appear in excessive amount in the urine apart from any obvious disease of the liver, because the quantity of urobilin carried to the liver from the intestine being so much increased, the fraction carried past the liver into the general circulation and so to the kidneys is sufficient to lead to an obvious urobilinuria.

4. There is a close association between increase of urobilin in the urine and disturbance of liver function. But even if increased blood destruction is excluded by urobilin estimations in the stools, it is not at present possible to regard the amount of urobilin in the urine as an approximate guide to the functional efficiency of the liver. The occasional occurrence of large amounts of urobilin in the urine of patients in whom there is no reason to suspect damage to the liver, the great and irregular fluctuations of urobilin excretion in cases of liver disease from hour to hour and from day to day, and the want of knowledge as to the fate of urobilin in the blood and tissues make it necessary to recognize that there may be other factors besides the condition of the liver and the amount of blood destruction which influence the excretion of urobilin in the urine.

B. Clinical

Before discussing the clinical importance of the phenomena of urobilin elimination, we should like to draw particular attention, (1) to the insufficiency of our present quantitative methods of urobilin estimation, especially in the urine, and to state that they undoubtedly will be very difficult to overcome because of the marked instability of the group of substances included under this name; and (2) to the value, until now insufficiently appreciated, of estimations of urobilin in the stools as a guide to the amount of blood destruction in the body.

The interpretation of urobilin findings in the urine is interesting, but at present somewhat problematical, whereas the determination of an increased intestinal excretion rests on a much firmer basis, and should yield results of diagnostic importance.

Since this work was undertaken with the primary object of finding out just how much significance should be attached to the presence of abnormal quantities of urobilin and urobilinogen in the excretions in ordinary clinical work, we shall summarize briefly our conclusions, basing them on our own experimental studies, clinical observations and a fairly exhaustive study of the literature. The difficulty of the problem has been to form a judgment as to how far one is able clinically to make assertions from the data at present obtainable. To choose the essential facts from the maze of non-essential detail and from the numerous observations made to substantiate a previously accepted theory has been difficult. Nevertheless, we feel that we are within safe limits in the following conclusions as to the significance of the presence of abnormal quantities of urobilin in certain pathological conditions.

1. *Hepatic Cirrhosis.*—Urobilinuria is of marked value as evidence of a definite pathological change in the enlarged liver of alcoholic persons and occurs almost constantly in the hypertrophic stage of hepatic cirrhosis. In our cases, we did not find any increase of urobilin in the stools. While in advanced cases, part of the urobilin in the urine may be derived from the formation of urobilin from bilirubin in the liver, it is probable that as a rule it is due to failure on the part of the liver to synthesize to bilirubin, the urobilin brought to it from the intestine.

2. *Hepatic Stasis.*—Estimations of urobilin in the urine are of value in judging the amount of damage done to the liver parenchyma by chronic passive congestion. Hence, a marked increase of it is of ominous prognostic significance in cardiac decompensation.

3. *Jaundice.*—Urobilinuria is absent or insignificant in cases of obstructive jaundice. Its intermittent occurrence points to an incomplete obstruction with concomitant damage to the liver. It is present in the icterus of cases of increased destruction of the red blood-cells. Careful studies for urobilin should be made in suspected cases of chloroform poisoning, acute yellow atrophy and other similar conditions in which the liver is apt to be damaged.

4. *Malaria.*—The great increase of urobilin in the stools and the urobilinuria which occurs in severe cases of malaria is of diagnostic importance in obscure febrile conditions. The persistence of urobilinuria after malarial attacks, when there is no fever and no increase of urobilin in the stools, can be taken as evidence of some complication such as hepatic cirrhosis or abscess.

5. *Anemias.*—By means of urobilin estimations in the stools and urine, those forms of anemia associated with an increased blood destruction may be differentiated. It is probably in this field that the most valuable clinical results will be obtained. The contrast between the very large total urobilin elimination in our cases of pernicious anemia as compared with the small amount found in secondary anemias following hemorrhage or carcinoma was very striking.

6. *Pneumonia.*—A slight increase of urobilin with additional amounts at the time of resolution does not indicate a severe damage of the liver

parenchyma in this disease. It is probably due to a clogging of the liver with the products of resolution and absorbed hemoglobin from the affected lung. A study of the curve of this elimination may be of value in certain pneumonias. Allowances must always be made for other factors such as constipation, diarrhea and the inability of the kidney to eliminate urobilin readily in the presence of a complicating severe nephritis. The early appearance of large quantities of urobilin in the urine in pneumonia, particularly in the presence of jaundice, makes the prognosis grave. The occurrence of urobilin in the serum of pneumonia patients is of the gravest prognostic significance. It is recognized apparently by our present methods only in the presence of a degree of cyanosis markedly unfavorable to the life of the individual.

7. *Carcinoma.*—Except in those cases in which there is practically a complete disappearance of urobilin from the excretions, due to an obstruction of the common duct from carcinoma, we have not found its estimation in carcinomatous cases to be of evident clinical value.

8. *Infections.* — In infectious processes causing parenchymatous changes in the liver or accompanied by hemolysis, urobilin estimations are of definite value in estimating both of these factors in any given case. There is apparently an approximation between the urobilin excretion in the urine and feces and the amount of blood destruction. In such infectious processes as amebic colitis, the appearance and constant presence of urobilin may be of marked value in indicating the presence of inflammatory liver conditions, particularly abscess.

9. *Scarlet Fever, Measles.*—The majority of measles cases present urobilinuria in excess, but, as might be expected, the amount is less and the duration shorter than in scarlet fever with its more definite damage to the hepatic cells.

10. *Decompensation.*—As indicated previously, marked urobilinuria is indicative of pathological change in the liver in the stasis of decompensation. This circulatory stasis calls for the use of increasing amounts of hemoglobin within the body and is associated with a greater production and elimination of bilirubin leading to an inability on the part of the overburdened and congested liver to modify the abnormal amounts of urobilin reaching it. A return of compensation is often indicated by the disappearance of a qualitative urobilinogen or urobilin test. Decompensations in markedly anemic persons are not so apt to be accompanied by increased amounts of urobilin until very profound stasis occurs.

11. *Nephritis.*—Severe nephritis of various types, even in the presence of increased production of urobilin, may prevent definite urobilinuria. Large amounts of urobilin in the urine may be taken as indirect evidence of a certain degree of efficiency in the renal epithelium.

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THE EFFECT OF HEAT ON BLOOD-PRESSURE *

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In most infectious disease there is a progressive fall in blood-pressure during the course of the infection. This fall has been attributed to a weakness or insufficiency of the circulatory apparatus. In 1899 Romberg, Pässler, Bruhns and Müller[1] investigated the cause of this presumed weakness by means of animal experiments. They reached the conclusion that the myocardium was not at fault but that the toxin of the infection caused a grave injury to the vasomotor center in the medulla, and that the low pressure was due entirely to an abeyance of the function of this center. Since that time it has been generally held by clinicians that the height of the blood-pressure in the infectious diseases was a measure of the tone of the vasomotor center, that low readings were evidence of the failure of the center and were an absolute indication for therapeutic procedures which stimulated the center.

During the past year one of us (L. H. N.) has been studying, at the Massachusetts General Hospital, the therapy of the circulatory disturbances in the acute infections based on these principles. The results, on the whole, have been such that it seemed desirable to reinvestigate this phase of the problem.

Increased body temperature is a symptom of all infections. Romberg and Pässler[1] failed to eliminate the effect on the blood-pressure of this constant factor. It therefore remains undecided whether the hypotension observed by them was due to toxins, fever, or both.

In the experiments on which this paper is based the effect of increased body temperature, in the absence of infection, was studied in order that its importance as a factor in causing the lowered blood-pressure of infection might be determined.

Halliburton in 1901[2] pointed out that all tissues contain a protein which coagulates between 45 and 50 C. (113 and 122 F.), that during

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[1] Romberg, Pässler, Bruhns and Müller: Experimentelle Untersuchungen über die allgemeine Pathologie der Kreislaufstörung bei acuten Infectionskrankheiten, Arch. f. klin. Med., 1899, lxiv, 652.

[2] Halliburton, W. D.: Chemical Side of Nervous Activity, Croonian Lectures. London, 1901, p. 42.

heat rigor the first shortening of mammalian muscle occurs at 47 C. (116.6 F.), and that it loses its irritability—that is, is physiologically dead —at that point. Marinesco[3] has shown that a temperature at 45 C. (113 F.) kills animals in from one to two hours, and 43 C. (109.4 F.) in a longer time; and that the occurrence of death is coincident with the breakdown of the nerve-cells. Halliburton[2] found that saline extracts of brains kept at a temperature of 44 C. (11.2 F.) show a precipitation of globulin after two hours. When the temperature is 42 C. (107.6 F.), the precipitation occurs in from three to four hours. A temperature of from 40 to 41 C. (from 104 to 105.8 F.) causes no coagulation after eight hours. Thus we see that degrees of hyperthermia occasionally seen in infections cause morphological changes in nervous tissue, and that lower temperatures produce effects identical with higher ones if the former obtain over longer periods of time.

One of the factors which is necessary to maintain an efficient blood-pressure is a constant constriction of the arterial tree. To maintain this constriction there must exist not only an active nervous system, but also smooth muscle capable of responding normally to stimuli. The relaxing effect of heat on smooth muscle is well known and must be taken into account when considering the effect of heat on blood-pressure. It has recently been noticed by clinical observers[4] that the blood-pressure is lowered during the application of heat in the form of hot baths or similar maneuvers in nephritis, etc. It is not known whether the body temperature was raised as a result of this form of treatment.

Our experimental procedure was as follows: Rabbits and cats were anesthetized with urethane (ethyl carbamate) employed in a dosage of 2 gm. per kilogram, given by stomach-tube. Occasionally an additional gram of urethane was required in order to obtain complete anesthesia. Blood-pressure was written from the carotid artery by means of a mercury manometer. The animals were placed in a copper tank which contained sufficient water at body temperature to cover the animal except its head. The water was heated by means of an insulated electric resistance-coil in the bottom of the tank. The temperature of the water and the animal's rectal temperature were recorded. Fourteen experiments were performed.

In the first group of experiments the temperature of the animals was rapidly raised. The first effect of the heat was a progressive rise in blood-pressure. At a temperature of between 108 and 110 F., varying

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[3] Marinesco: Quoted by Halliburton.

[4] Lawrence, C. H.: The Effect of Pressure-Lowering Drugs and Therapeutic Measures on the Systolic and Diastolic Pressures in Man, THE ARCHIVES INT. MED., 1912, ix, 409.

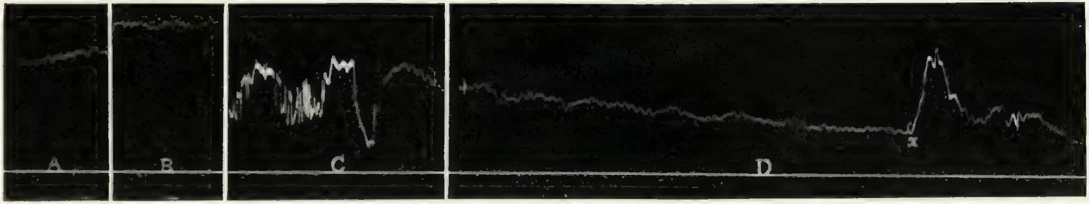

Fig. 1. Experiment 10.—The upper line is the carotid blood-pressure; the lower line is 50 mm. Hg pressure. *A* shows the pressure at the beginning of the experiment. The record of the next fifty minutes is omitted. *B* is the tracing obtained from the fiftieth to the sixtieth minute. The cat's temperature was rising from 103.7 to 104.5 F. The temperature of the water was 107.6 F. The respiration was too rapid to count accurately about 400 per minute—shallow, panting, but still regular. At *C* the wide variations occurring toward the end of the second hour—the one hundred and fifth to the one hundred and twentieth minute are shown. The cat's temperature was from 108 to 108.5 F. The temperature of the water was 109 F. The respiration was more than 400 per minute, shallow and irregular, but the mucous membranes were pink. *D* represents the last forty-five minutes of the experiment—from the one hundred and thirty-fifth to the one hundred and eightieth minute. It showed a steady fall in pressure broken only by the response to asphyxia at *X*. The small amplitude of the pulse is noteworthy. During this period the cat's temperature rose slowly from 108.9 to 110 F. The temperature of the water was 109 F. During the third hour the respiratory rate has been slowly decreasing and had fallen to 120 per minute just before the effect of asphyxia was tried. It was constantly irregular.

with the individual, the pressure began to fall and continued to do so until the end of the experiment. Experiment 10 is cited in detail as an example of this group.

Experiment 10.—July 28, 1913, a female cat weighing 4 kg. was given 8 gm. of urethane by stomach-tube at 10 a. m. A cannula was inserted into the left carotid artery, and a cannula into the trachea. A thermometer was inserted as high as possible into the rectum. The animal was transferred to the tank containing water at a temperature of 99.5 F. at 10:45 a. m. A continuous record of the blood-pressure was written. Table 1 shows the temperature of the water, the rectal temperature of the cat, the blood-pressure level and the rate and character of the respiration, marked off in approximately five-minute periods throughout the experiment.

TABLE 1.—Record of Experiment 10

Time. A. M.	Temp. Water, F.	Temp. Cat, F.	Blood-Pressure mm. Hg	Respiration
10:55-11:00......	99.7	100.0	155	66
11:00-11:03......	100.4	100.2	150	94
11:09-11:15......	103.0	101.0	150	160
11:15-11:20......	104.0	101.0	144	160
11:20-11:25......	105.8	101.9	150	260; shallow, panting.
11:25-11:30......	107.6	102.0	155	400; regular, panting.
11:30-11:35......	107.6	103.0	162	400; regular, panting.
11:35-11:40......	107.6	103.7	174	400; regular, panting.
11:40-11:45......	107.6	104.5	174	400; regular, panting.
11:45-11:52......	107.6	104.5	*	400; regular, panting.
11:52-12:00......	.....	106.4	126	400; irregular.
P. M.				
12:05-12:25......	107.6	†		
12:25-12:30......	108.6	107.5	110-136	400; irregular.
12:30-12:35......	109.0	107.5	88-142	Too rapid to count.
12:35-12:40......	109.0	108.0	90-148	Too rapid to count.
12:40-12:45......	109.4	108.2	70-140	Too rapid to count.
12:45-12:50......	109.4	108.2	100-120	Too rapid to count.
12:50-12:55......	109.4	108.2	88-112	Very irregular.
12:55- 1:00......	109.4	108.5	110	Very irregular.
1:00- 1:05......	109.4	108.9	124	Slower.
1:05- 1:10......	109.4	109.1	117	Slower.
1:10- 1:15......	109.4	109.6	106	Slower.
1:15- 1:20......	109.4	110.0	96	Slower.
1:20- 1:25......	109.0	110.0	86	120
1:27	109.0	110.0	84-154	Asphyxia reaction.
1:30- 1:35......	109.0	110.0	70-100	66; deep; regular.
1:35- 1:40......	109.0	110.0	67	52-36; deep; cyanosis.

* Clot removed.

† Clot. Cannula in right carotid.

The animal's temperature was raised from 100 to 104.5 F. in the course of the first hour. The pressure during this period rose from 144 to 174 mm. Hg. During the second hour the temperature rose from 104.5 to 108.2 F. The pressure showed wide variations with a general downward tendency. The heart had become markedly irregular and the steep falls in pressure are evidence of this condition. Respiration became too rapid to count — more than 400 per minute — irregular and shallow. During the third hour the temperature rose from 108.2 to 110 F. The pulse had become very small but more regular. There was a progressive fall of blood-pressure to 64 mm. Hg. The respiratory rate slowly decreased but its character remained the same. At X (Chart 1) a rubber tube 1½ feet long was attached to the tracheal cannula. As is well known, asphyxia is one of the most powerful stimulants to the vasomotor center. The pressure rose from 84 to 154 mm. Hg — a response of 70 mm. The respirations became deep, regular and slow, falling to thirty-six per minute.

It may well be questioned whether the fall of pressure was not a result of great interference with the function of living tissue brought about by the extreme heat. In favor of this view we have the great cardiac irregularity and the very rapid, irregular respiration, which then becomes slower with increasing heat. On the other hand, the asphyxial rise in pressure indicates that the vasomotor reflex was still intact. But since it was primarily our object to investigate the effect of degrees of heat which are the rule in infections, we performed further experiments in which the heat was not allowed to become excessive. Experiments 7 and 11 are cited as examples of this group.

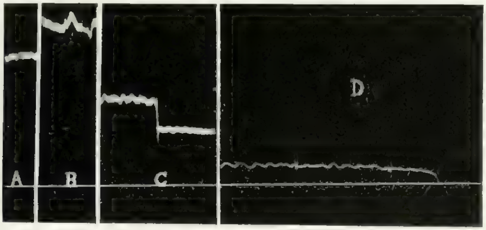

Fig. 2. Experiment 7.—The upper line is the carotid blood-pressure. The lower line is 50 mm. Hg pressure. *A* is the pressure at the beginning of the experiment. The cat's rectal temperature was 100 F. At *B* the pressure is shown forty-five minutes from the beginning of the experiment. The cat's rectal temperature was 104.5 F., that of the water 105.8 F. Respiration was 260 per minute. At *C* the pressure one hour, and one hour and ten minutes, from the beginning of the experiment is shown. The cat's temperature was from 104.5 to 105.3 F., the temperature of the water between 105.8 and 106.8 F. The respiration had fallen progressively from the beginning of the experiment and was now between 176 and 208 per minute. The pressure had fallen 92 mm. during the previous twenty-five minutes and was 62 mm. lower than at the beginning of the experiment. The cat's temperature remained between 105.5 and 106 F. for the next hour and twenty minutes, at the end of which time the respiration, which had become steadily slower, suddenly ceased. The pressure fell slowly during this period from 96 mm. to 65 mm. *D* represents the last ten minutes of the experiment.

Experiment 7.—July 19, 1913, a male cat, weighing 4.2 kg. was given 8 gm. of urethane by stomach-tube at 9:20 a. m. A cannula was inserted into the carotid artery and a thermometer inserted as high as possible into the rectum. At 10:15 a. m. the animal was placed in the tank containing water at a temperature of 99.5 F. For the next forty minutes the water was rapidly heated until it reached 105.8 F. During the rest of the experiment it was kept between 105 and 106.8 F. Table 2 shows the temperature of the water, the rectal temperature of the cat, the blood-pressure level and the rate and character of the respirations throughout the experiment. The time notations in the first column represent periods when the drum was revolving.

TABLE 2.—Record of Experiment 7

Time, A. M.	Temp. Water, F.	Temp. Cat, F.	Blood-Pressure mm. Hg	Respiration
10:17-10:20......	99.5	100.0	158	280
10:35-10:38......	104.0	102.0	176	260
10:58-11:01......	105.8	104.5	188	260
11:15-11:18......	105.8	104.5	122	208; shallow, irregular.
11:28-11:31......	106.8	105.3	96	176; shallow, irregular.
11:35-11:40......	106.2	105.5	90	176; shallow, irregular.
11:40-11:45......	106.2	105.5	88	176; shallow, irregular.
11:45-11:50......	105.8	105.5	84	144; shallow, regular.
11:50-11:55......	105.8	105.5	84	144; shallow, regular.
P. M.				
12:00-12:05......	106.1	105.5	74	144; shallow, regular.
12:05-12:10......	106.1	105.5	74	144; shallow, regular.
12:10-12:15......	106.1	105.5	72	144; shallow, regular.
12:15-12:20......	106.1	105.5	72	144; shallow, regular.
12:20-12:30......	*			
12:30-12:35......	106.7	105.5	65	144; shallow, regular.
12:35-12:40......	106.7	106.0	65	111: shallow, regular.
12:40-12:45......	105.8	106.0	65	100: shallow, regular.
12:46	105.8	106.0	65-0	64; shallow, regular.
12:48	105.8	106.0	...	Ceased.
12:50	†			

* Clot removed.
† Heart stopped.

Experiment 11.—July 31, 1913, a male cat weighing 4 kg. was given 8 gm. of urethane at 9:15 a. m. by stomach-tube and 1 gm. at 10:15 a. m. A cannula was inserted into the left carotid artery. The left cervical vagus trunk was dissected free and cut. A thermometer was inserted high into the rectum and the animal placed in the water at a temperature of 99.5 F. The central end of the vagus was then stimulated with an induction current of increasing strength until something greater than the threshold value had been reached. This strength of current was used throughout the experiment. The water was now rapidly heated to 104 F. and kept at this temperature for the next eight and one-half hours. The blood-pressure was written approximately once an hour during this period. After the drum had been revolving for several minutes the central end of the vagus was stimulated with the induced current. The nerve was then carefully replaced between the tissues to be kept fresh. Several times the nasal mucous membrane was stimulated.

The group of experiments of which 7 and 11 are types show a well-marked fall in blood-pressure due to a degree of hyperthermia not exceeding that encountered in infections. In all cases the fall occurred before any organic changes due to hyperthermia could be expected to occur. As is seen in Experiment 12, which was performed as a control, no such fall occurred when the animal, kept at a normal temperature, was subjected to all other conditions of the experiment.

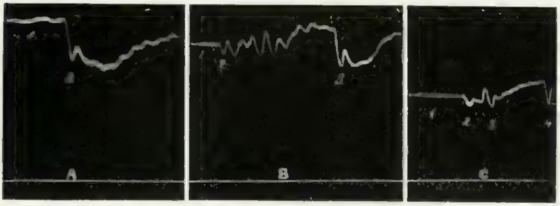

Fig. 3. Experiment 11.—The top line is the carotid blood-pressure. The next line is 0 mm. Hg pressure. Portions of the record from the beginning of the experiment, three hours later, and eight and one-half hours later, are shown: 1, *A*, is the initial level of blood-pressure, 136 mm.: 2, *A*, is the response to vagus stimulation when the pressure is 136; the pressure fell 40 mm.: 1, *B*, is the blood-pressure level, 114, after three hours: 2, *B*, is the response to vagus stimulation when the pressure is 114: the pressure fell 9 mm.: 3, *B*, is the response to vagus stimulation when the pressure is 128; the pressure fell 32 mm.: 1, *C*, is the blood-pressure level, 72, after eight and one-half hours: 2, *C*, is the response to vagus stimulation when the pressure is 70: the pressure fell 7 mm.; 3, *C*, is the response to vagus stimulation when the pressure is 80; the pressure fell 17 mm.; 4, *C*, is the response when the pressure is 84; the pressure fell 29 mm.

TABLE 3.—Record of Experiment 11

Time, A. M.	Temp. Water, F.	Temp. Cat, F.	Resp.	B. P. mm. Hg	Response to Stimulation
11:20-11:33	98.6	99.5	48	136	Vagus 10 sec. 136— 96 = 40
P. M. 12:25-12:35	104.0	102.5	214	114	Vagus 1 sec. 113—110 = 3
					Vagus 3 sec. 116—107 = 9
					Vagus 10 sec. 110— 99 = 11
					Vagus 10 sec. 128— 96 = 32
1:25- 1:35	104.0	103.2	150	118	Vagus 10 sec. 119—115 = 4
					Vagus 10 sec. 114— 99 = 15
					Vagus 10 sec. 130—112 = 18
					Vagus 10 sec. 130—103 = 27
2:25- 2:35	104.0	103.0	150	114	Vagus 10 sec. 114—105 = 9
					Vagus 10 sec. 128— 96 = 32
3:25- 3:30	104.0	103.2	106	104	Vagus 10 sec. 105— 97 = 7
4:35- 4:40	104.0	103.2	106	100	Vagus 10 sec. 98— 85 = 13
5:35- 5:40	103.6	103.2	106	87	Vagus 10 sec. 88— 74 = 14
					Nose 10 sec. 88—109 = 21
6:40- 6:45	103.6	103.2	100	76	Vagus 10 sec. 78— 62 = 16
					Nose 10 sec. ? ?
7:40- 7:53	104	103.2	100	72	Vagus 10 sec. 70— 63 = 7
					Vagus 10 sec. 79— 62 = 17
					Vagus 10 sec. 84— 64 = 20

Experiment 12.—Aug. 6, 1913, a male cat weighing 4.2 kg. was given 8 gm. of urethane by stomach-tube at 9 a. m., 1 gm. at 9:30 a. m., and 1 gm. at 9:55 a. m. A cannula was inserted into the left carotid artery, and a thermometer high into the rectum. The cat was placed in a tank containing water at 100.4 F. at 10:15 a. m. The cat's temperature fell from 100.4 F. at 9:30 a. m. to 98 F. at 10:15 a. m.

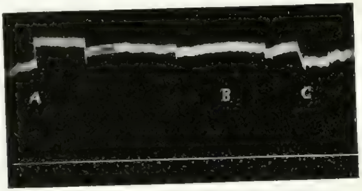

Fig. 4. Experiment 12.—The upper line is the carotid blood-pressure; the lower line is 50 mm. Hg pressure; *A* is the initial pressure, *B* the pressure after one hour, and *C* the pressure after two hours. This tracing shows the practical absence of change in the blood-pressure level when the animal is kept in water at body temperature.

TABLE 4.—Record of Experiment 12

Time, A. M.	Temp. Water, F.	Temp. Cat, F.	Blood-Pressure mm. Hg	Respiration
10:20-10:25......	100.4	98.6	136	36
10:30-10:32......	100.4	98.6	150	36
11:00-11:05......	100.4	100.4	144	40
11:30-11:35......	98.6	99.5	144	40
12:20-12:25......	100.4	100.0	136	40

It appears, therefore, that the fall in pressure was entirely due to the effect of heat on the organism.

DISCUSSION

Our chief interest centers about the fall in pressure which results from degrees of heat of not uncommon clinical occurrence. We know from daily observation that such amounts of hyperthermia do not cause serious organic damage. The hypotension of such conditions, therefore, must be evidence of a functional disturbance.

Since blood-pressure is determined by the energy of the heart as measured by the output per minute against resistance, and on the other hand by peripheral resistance, it is evident that the low pressure might be due to a lessened output from the heart, or to a diminished peripheral resistance, or to both; and the lessened peripheral resistance in turn might result from relaxation of the smooth muscles of the arterioles due to the heat, or to fatigue of the nerve-cells in control of the vascular mechanism. The factors affecting peripheral resistance may be considered first.

It has long been held by clinicians that heat has a marked relaxing effect on smooth muscles, but they have consciously or unconsciously thought of this effect in relation to muscle which is undergoing abnormal tonic or clonic contractions. We know of no clinical evidence which may be presented to show that heat has the same effect on smooth muscle in a state of normal tonicity. DeZilwa[5] and Stewart[6] have shown experimentally that there is a gradual relaxation of the tone of smooth muscle as the temperature is raised from 10 to 40 C. (from 50 to 104 F.), but that temperatures over 40 C. cause a shortening again. In their experiments the amount of change occurring between 38.5 and 40 C. (101.3 and 104 F.) is very small. If we seek to explain our results as examples of the decrease of tonicity of smooth muscle in response to heat, we should expect to find that the pressure fell as the temperature rose to 40 C. (104 F.), and that the pressure rose thereafter with increasing temperature. Examination of our tables will show that just the opposite occurred. Therefore, we cannot logically attribute the hypotension to this factor.

In considering the other possible factor that might diminish peripheral resistance, we have to take into account the conditions of activities of nerve-cells. It is highly characteristic of nervous activity that periodic rest is needed to restore normal function. The observations of Hodge[7] showed that in nerve-cells definite physiological changes develop during the day and are recovered from during the rest at night. "Continuous loss of sleep is far more rapidly fatal than starvation, and the final changes, especially in the nervous system, are very marked" (Donaldson[8]). Howell has shown that sleep is accompanied by a diminution of vascular tone, that is, a lessened activity of the vasomotor center. Since, therefore, there is this alternation of fatigue and recovery through long periods during the twenty-four hours, and since the absence of the resting period is known to be harmful to the nerve-cells, the necessity for repair in these cells is obvious.

Studies of the effect of temperature on chemical processes have shown that there is approximately an increase of 10 per cent. in the speed of reaction with every increase of 1 degree centigrade. The metabolic processes occurring in nerve-cells are chemical in character, and a number of observations are on record to show how markedly the speed

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5. DeZilwa: Quoted by Grützner. Ergebn. d. Physiol., 1904, ii, 12.
6. Stewart, C. C.: The Cat's Bladder, Am. Jour. Physiol., 1900, iv, 185.
7. Hodge: Quoted by Donaldson, The Growth of the Brain, London, 1895, p. 317.
8. Donaldson, H. H.: The Growth of the Brain, London, p. 309.

of nervous activity is augmented by increased temperature. Thus Helmholtz[9] found the velocity of the nerve impulse in the frog at 0 C. (32 F.) to be 2.7 meters per second; at 20 C. (68 F.) 27 meters per second. Von Miram[9] found the rate for the frog 0.24 meters per second at 20 C., and 65 meters at 35 C. (95 F.).

Since the evidence from activity and rest indicates that during the active period the catabolic changes are more rapid than the anabolic, it is highly probable that similarly increased heat has a greater effect on the catabolism of the neurons than on the anabolism. The increased speed of the catabolic processes which heat would induce might, therefore, result in increased tone of the vasomotor center in the early stages, and that period might be followed by a later period of diminished tone because of approaching exhaustion of the nerve-cells.

W. T. Porter[10] and his associates have brought forward evidence which indicates that the tone of the vasomotor center is not lowered by prolonged peripheral stimulation. Such stimulation, however, becomes widely dispersed through the nervous system and only in part affects the vasomotor center. Heat, one the other hand, would have as much effect on one cell as on another, and the fact that increased heat is accompanied by diminution of the tonic innervation of skeletal muscle indicates the possibility that a similar condition prevails in the vasomotor center.

In two of our experiments we tested the reflex response of the vasomotor mechanism after we had obtained large falls in blood-pressure. In every case the normal response occurred, but this evidence does not permit us to draw conclusions as to the tonus of the vasomotor cells, for Porter[11] has shown that the condition of the vasomotor center does not determine the presence or absence of the vasomotor reflex, and that consequently testing the reflex gives no information about the state of tonus of the center.

There still remains to be considered the effect of the heart rate on the lessened blood-pressure observed during continued hyperthermia. Experiments[12] have shown that the faster the heart beats the shorter the diastole, but within wide limits the abbreviation of the diastole occurs only in that part of it which has been designated diastasis; that is, the period of repose; and does not affect the period of relaxation or filling. If the heart is supplied with blood, a more rapid beat within the period of diastasis results in a greater output. Only when the beat becomes so rapid as to encroach on the period of filling does the output fail to vary with the rate of beat. The observations, reported in this paper, of increased blood-pressure in the early stages of hyperthermia and lessened blood-pressure after the temperature rose higher, are quite in harmony with the greater output from the heart that would result so long as the rapid beat encroached only on the period of diastasis, and with the lessened output that would result as the still more rapid beat would cause an encroachment on the period of relaxation or filling.

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[9] Helmholtz and Von Miram: Quoted by Snyder, Am. Jour. Physiol., 1908, xxii, 179.

[10] Porter, W. T., Marks, H. K., and Swift, J. B.: The Relation of Afferent Impulses to Fatigue of the Vasomotor Center, Am. Jour. Physiol., 1907, xx, 444.

[11] Porter, W. T.: Relation of Afferent Impulses to the Vasomotor Center, Am. Jour. Physiol., 1910, xxvii, 276.

[12] Henderson, Y.: A Principle Underlying the Normal Variations in the Volume of the Blood-Stream, Etc., Am. Jour. Physiol., 1909, xxiii, 353.

This review of evidence indicates that the heat probably does not cause sufficient local relaxation of smooth muscle in the arterioles to account for the low pressure. As between a central effect of the heat on the tonus of the vasomotor center and a peripheral effect on the heart, our observations thus far do not permit us to pass judgment. Quite conceivably both factors are involved in the production of effects which we have here reported, and as the foregoing discussion has shown, heat would operate in the same direction with both these factors to cause first a rise and later a fall of arterial pressure. For the present, therefore, we must leave open the explanation of our results and merely report the facts of observation.

CONCLUSIONS

1. In lower animals degrees of hyperthermia not greater than those encountered in infections are sufficient to cause marked hypotension.

2. The increased body temperature of infection is a potent factor in the production of the lowered blood-pressure which occurs in such conditions.

3. The hyperthermia may be the entire cause of such hypotension.

We are grateful to Dr. W. B. Cannon for having suggested the possible effect of heat on blood-pressure to us and for having aided us with many of the technical difficulties.

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PAROXYSMAL AURICULAR FIBRILLATION *

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The abnormalities of the cardiac mechanism which are responsible for various forms of cardiac arhythmia and disturbances in cardiac rate are now well understood, and have been especially well demonstrated by means of the string galvanometer. The analysis of disturbances of the cardiac mechanism, although of ever increasing diagnostic and therapeutic importance, is a field for original investigation which is fast losing its fertility. On the other hand, large problems lie before us in determining the essential causes of these cardiac disturbances. The progress of the treatment of cardiac disorders will be accelerated by the discovery of the now unknown changes, either within the heart or outside of it, which are responsible for these abnormalities of the cardiac mechanism. This is especially true of the large group of disorders characterized by disturbances in the generation of stimuli of the heart beat. These disturbances may predominate either in the auricles or in the ventricles, and may result in the occurrence of premature ectopic beats (extrasystoles), tachycardia of ectopic origin, the so-called auricular flutter or auricular fibrillation. These disturbances may occur in hearts already the site of anatomical lesions, but they may also occur in hearts which give no signs of such lesions.

It is with the hope that some light may be thrown on this question of the essential cause of disturbed excitability or stimulus formation that the following case of paroxysmal auricular fibrillation is reported.

CASE REPORT

History.—I. G., Hospital No. 601, a jeweler, aged 50, born in Russia, was admitted to the hospital Feb. 23, 1912, complaining of cardiac palpitation and weakness. He knows of no cases of cardiac disease or rheumatism in his family, and the family history is otherwise negative. The patient had been a generally healthy man, but always "high strung" and rather nervous. He thought that he had neither scarlet fever nor diphtheria in childhood, but since the age of twelve he had frequent attacks of tonsillitis, and at the age of 15 typhoid fever. When 18 years old he had an apparently rather mild attack of gonorrhea, but there never had been any other venereal affection. His wife is living and well, and they have several healthy children. He had considerable distress after eating for many years, and had always taken large amounts of food, especially bread, and much tea. He used both alcohol and tobacco moderately and had never done laborious work. He never had rheumatism, but there was pain without swelling or redness in the right shoulder, beginning about eleven years ago and lasting fifteen months. He continued his occupation as a jeweler with very little interruption up to a few weeks before admission to the hospital.

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* From the Hospital of the Rockefeller Institute for Medical Research, New York.

The present illness began twelve years ago, in 1900, when the patient felt undue fatigue after exertion, and on the following day he had his first attack of cardiac palpitation and weakness, much like that for which he came to the hospital. He was in bed for three days at this time. He then had no such symptoms for about eighteen months, when the second attack occurred, and since then he has had similar attacks, usually lasting only a few hours, every four to six months. Occasionally they have lasted as long as three days. The patient thinks that the gastric disturbance, noticed especially after eating, had something to do with causing the attacks of palpitation. About eight weeks before admission the patient had the first of the series of attacks which brought him to the hospital. The first attack began Dec. 22, 1911, in the usual way, with a boring feeling in the epigastrium, a thumping feeling now and then in the heart, and finally a sudden onset of cardiac palpitation. There was also a feeling of pressure about the chest, and choking, headache and weakness. This attack lasted twenty hours and stopped suddenly. During the next three weeks the patient had two or three attacks of lesser severity, and then, Jan. 13, 1912, an attack began which lasted three and a half days. This was followed by four days when the patient felt quite well, at the end of which time the symptoms returned and continued for seven days. Then he was free from symptoms for ten days, when another attack, lasting a few days, occurred. Finally, after the patient had been feeling well for nearly two weeks, the final attack before admission began, and this time in an unusual way, a feeling of palpitation coming and going for a day or so, and then settling down on February 22, the day before admission, to what seemed to the patient a severe attack. Besides the symptoms that have been mentioned he had moderate pain in the left arm and in the back of the neck. He was able to walk into the hospital, but with some difficulty.

Physical Examination.—Physical examination showed the patient to be a rather poorly nourished, small man, who looked at least ten years younger than his age. He was lying quietly and apparently comfortably in bed, but appeared somewhat nervous. He was alert and highly intelligent. The eyes showed normal pupillary reactions to light and accommodation. The fundi were apparently normal except for slight tortuousness to the arteries. The tonsils were not enlarged. There was slight venous pulsation in the neck. The thyroid was not palpable. The lungs yielded normal physical signs throughout. There were no abnormal pulsations seen over the thorax, while there was a general heave in the region of the left nipple. The precordium was not prominent. The apex beat was in the fifth space, 10 cm. to the left of the midsternal line. The outline of cardiac dulness extended 4.0 cm. to the right of the midsternal line in the fourth space, and 11.5 cm. to the left of the fifth space. The heart sounds were clear throughout, no murmurs being heard. The second pulmonic was slightly accentuated, and had a liquid quality. The radial pulse was distinctly irregular, and had a rate of about 75 per minute. Many of the pulsations were well sustained, but they were irregular in both force and rhythm. The actual heart-rate as counted by auscultation over the heart was 126 per minute. The arteries were distinctly palpable in the arm, at the wrist and especially at the elbow. The temporal arteries were also indefinitely palpable. The abdomen was normal. Neither liver nor spleen was palpable. There was no edema of the extremities. Blood, hemoglobin 95 per cent. (Sahli) corrected reading = 119 per cent. Wassermann reaction was negative. The urine showed neither albumin nor casts. Its specific gravity was 1.030. The amount was 650 c.c. in twenty-four hours. Electrocardiograms showed that auricular fibrillation was present (Fig. 1.)

Subsequent Course.—Digitalis was begun three days after admission, and in three days distinct slowing of the ventricles had occurred and the arhythmia was much less marked. March 1, at 10:30 a. m., the patient was bled from an arm vein and 40 c.c. of blood was obtained. At 11 a. m. he noticed a sudden change in the feeling of the heart beat, and declared that his attack was over. The examination revealed that the patient's heart was beating regularly, at first at a rate of 108, and in a few hours at about 90. The outline of relative cardiac dulness extended 4 cm. to the right in the fourth space, and 10 cm. to the left in the fifth space. The heart sounds were clear and of good quality all over the precordium. There were no murmurs, but the second aortic sound was accentuated. The patient felt immediately distinctly more comfortable, and seemed to be entirely well except for slight weakness. Electrocardiograms showed that the normal sequential beat had returned (Fig. 2).

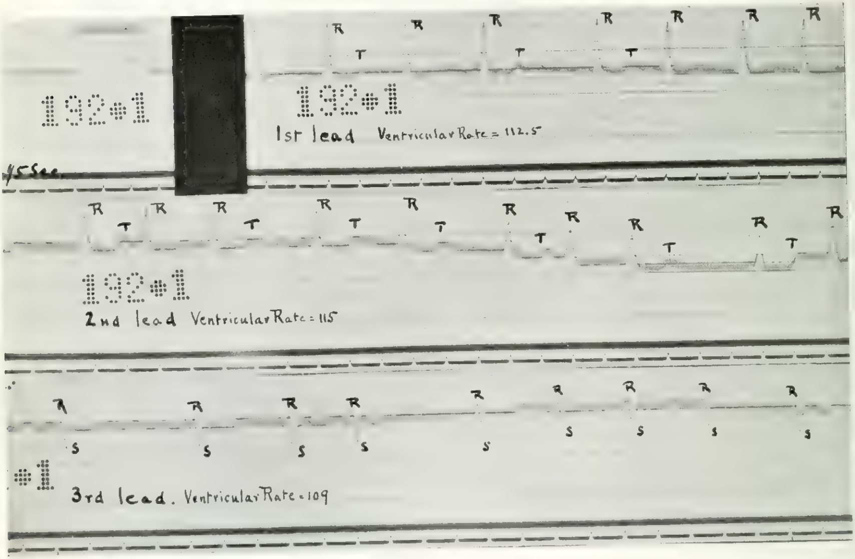
192#1
192#1
1st lead Ventricular Rate = 112.5
1/5 Sec.
192#1
2nd lead Ventricular Rate = 115
#1
3rd lead. Ventricular Rate = 109
R
T
S

Fig. 1.—Curves 192. February 25. First, second and third leads, showing auricular fibrillation. Ventricular rate averages 112 beats per minute. The time marking is always in 1/5 seconds.

During the night of March 6, after the heart had been beating normally for about sixty hours, the patient felt an occasional jumping feeling in the epigastrium, which he said usually occurred before attacks, and which led him on this occasion to predict the return of cardiac palpitation. During the night it was noticed that cardiac arhythmia existed for a few minutes on several occasions.

The heart continued to beat regularly, however, until March 10, when the patient awoke at 1 a. m. with the sensation of weakness and felt that his heart was beating irregularly. When examined at 9:30 a. m. the typical arhythmia of auricular fibrillation was present, the diagnosis of which was confirmed by electrocardiograms. This arhythmia continued until the afternoon of March 14, nearly five days. On this day the patient was restless, worried and especially uncomfortable in the morning, but in the afternoon the heart suddenly, practically instantly, became regular. The patient immediately felt much better, and except for muscular soreness and weakness was without symptoms. The cardiac examination gave results similar to those obtained during his first period of cardiac regularity. His condition remained excellent, and on March 22, after the heart had been regular for eight days, the patient was allowed to sit up out of bed for half an hour. March 23, a few minutes before 7 a. m., the pulse became suddenly irregular again. When seen a little later the patient was comfortable, and the heart, although completely irregular, was not beating very rapidly, and nearly all beats produced palpable radial pulsations. The heart sounds were clear. The arhythmia was still present on March 25, when the patient complained of feeling especially badly, with dizziness, weakness and a feeling of helplessness. On March 26, at about midnight, the patient awoke to find that his pulse was regular and rapid, and when examined the next morning the heart was beating perfectly regularly as before. The outline of relative cardiac dulness extended 2 cm. to the right and 11.5 cm. to the left in the fourth space, and the heart sounds were as before. The cardiac rate was 80. Electrocardiograms again showed that the auricles were beating normally, and were once more properly coordinated with the ventricles. The patient seemed in excellent condition without symptoms, and the heart maintained a rate of about 72 for

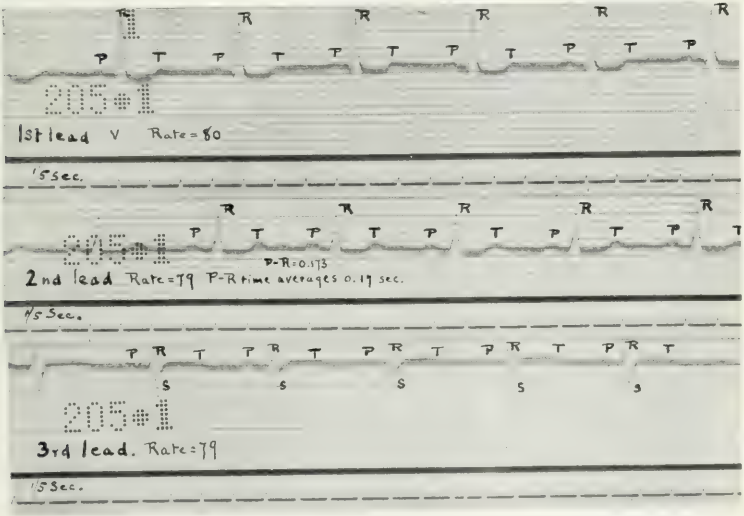

Fig. 2.—Curves 205. March 4. First, second and third leads obtained during the first period of cardiac regularity. The records show that the normal sequential beat is present. P.-R. time, second lead, average 0.17 second. Rate averages seventy-nine beats per minute.

several days. During the night of April 1, however, the patient had pain in the epigastrium and a feeling of suffocation, and on April 2, at 6 a. m., his pulse became suddenly irregular. When examined at 10 a. m., the heart was beating very irregularly, at a rate of about 140 per minute. Many beats failed to reach the wrist, and the radial pulse-rate was only about 100 per minute. The outline of relative cardiac dulness extended 3.5 cm. to the left in the third space, and 3.0 cm. in the fourth space, and 10.0 cm. to the left in the fourth space. The electrocardiograms were those of auricular fibrillation. From April 2 the cardiac arhythmia continued as long as the patient was under observation. The heart rate gradually slowed and became more nearly regular, but electrocardiograms showed that auricular fibrillation was still present when he was discharged on May 23, feeling quite comfortable and well. He had been walking about the ward for several days without symptoms. The arhythmia continued for several weeks after the patient left the hospital. It was subsequently learned that the patient died about two months later with symptoms suggesting acute dilatation.

DISCUSSION

During the time the patient was in the hospital he had three periods of nine, nine and six days, when the heart was beating regularly, between which auricular fibrillation occurred for five and four days. It was also present during the first six days and during the last fifty-one days in the hospital.

The change from one form of cardiac mechanism to another was usually sudden, but premonitory symptoms were sometimes noted by the patient before the onset of the arhythmia. These were, as have been described, a feeling of gastric distress and a thumping feeling in the cardiac region which was probably caused by the occurrence of premature ventricular contractions (extrasystoles). The occurrence of such beats was recorded by electrocardiograms several times during periods of fibrillation. The actual onset of auricular fibrillation occurred each time after the patient had been asleep, once apparently during sleep. On the first occasion the patient awoke at 1:00 a. m. with a sensation of weakness and felt that his heart was irregular, and the second and third occasions the arhythmia began suddenly at 7:00 a. m. and 6:00 a. m., respectively. Muscular exertion and psychic excitement, unless it was in dreams, played, therefore, no rôle in initiating auricular fibrillation. Gastric disturbance also did not seem to be a factor at such times. Thus, there was no evidence supporting the patient's statement concerning the influence of gastric distress on the cardiac rhythm, which may be a factor in the production of complete arhythmia, as v. Müller[1] has pointed out.

Auricular fibrillation changed to the normal sequential beat three times while the patient was in the hospital. The first change occurred at 11:00 a. m., half an hour after 10 c.c. of blood had been withdrawn from an arm-vein, the second during the afternoon following an uncomfortable and restless forenoon, while the third change occurred at midnight, apparently during sleep. The changes were always sudden, and as the conditions under which they occurred were so different, no conclusions as to the possible cause of the changes can be drawn. The blood-letting was thought to have been a possible factor, but it was repeated on April 22, after fibrillation had been present three weeks, without any change in the cardiac mechanism. The patient stated that the return to the regular rhythm usually occurred when he was quiet.

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[1] Müller, v.: The Nervous Affections of the Heart, The Archives Int. Med., 1908, i, 1.

The administration of digitalis may have been a factor in causing the disappearance of auricular fibrillation on two occasions. The drug was begun in the form of digipuratum tablets, 0.1 gm., three days after admission, five tablets the first day, decreasing one tablet each day. On February 29 the patient was nauseated after having had 1.5 gm. of digitalis, and the drug was discontinued at 3:30 p. m. The fibrillation ceased at 11:00 a. m. the next morning.

The drug was begun again in the same manner on March 11, two days after the onset of fibrillation, and continued for four days, when it was stopped after the sequential beat had returned. Small doses of the tincture, 0.2 c.c., three times a day, were given during this period of normal rhythm with the idea that it might assist in maintaining the regular beat, but on March 23 fibrillation again set in, and digipuratum was begun as before. This was continued for two days, and was discontinued after ten doses, as the patient complained of feeling dizzy and weak. Thirty-six hours after drug was discontinued, the normal beat again returned. The drug was withheld after the next onset of fibrillation had been present fifteen days, because it was felt that its administration probably had no effect in stopping the auricular fibrillation, and that the sequential beat would return spontaneously. As this did not occur, digipuratum was again administered. At this time and again later, it was given until nausea occurred, but produced no apparent effect on the auricular fibrillation. Digitalis was given primarily not with the idea of influencing the auricular activity, but because the rapid, irregular and insufficient ventricular activity present at the time of admission demanded it. In fact, as Mackenzie[2] and others have pointed out, digitalis may be apparently a factor determining the onset of auricular fibrillation. In our case fibrillation seemed prone to cease a day or two after the drug had been pushed to its physiological limit and discontinued. On one occasion fibrillation came on while small doses of the tincture were being taken.

The ventricular activity was favorably influenced by digitalis, and the rapid, irregular heart beat was reduced to a rate of about 80, and became almost regular, while fibrillation continued. During the periods of regular cardiac activity the electrocardiograms showed that there was no prolongation of the time of conduction from auricles to ventricles, the

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[2] Mackenzie: Digitalis, Heart, 1910-11, ii, 295.

P-R time in the second lead records averaging 0.17 seconds. This case does not lend support, therefore, to the suggestion put forward by Lewis[3] "that the slowing of the heart, when auricular fibrillation is present and digitalis is given, is due to an increase of a previously existing defect in the conduction to the ventricle of those impulses which are built up rapidly and irregularly in the auricle."

BLOOD-PRESSURE

The relation of changes in blood-pressure to changes in the cardiac mechanism was studied. The difficulty of determining the blood-pressure in cases of auricular fibrillation is evident, as the ventricular contractions, varying in force, produce variations in the blood-pressure from beat to beat. On account of the fact that exact estimations were impossible, the blood-pressure was not recorded at first, during auricular fibrillation, but later when the heart was beating more nearly regularly, the pressure was determined by the auscultatory method, at which the strongest beats produced sounds in the brachial artery and also at which practically all beats produced sounds. The average of these two readings was considered as the systolic blood-pressure. In a similar way two diastolic readings were taken and averaged. The blood-pressure readings are seen in the accompanying chart (Fig. 3). Although the blood-pressure was constantly high, marked changes took place, the systolic pressure varying from 125 to 215 mm. Hg. The diastolic pressure was more constant, but varied from 85 to 120 mm. Hg. In the second period of regular rhythm, from March 14 to 23, the blood-pressure rose gradually from 125 mm. Hg to 175, when fibrillation again set in. The blood-pressure did not fall with the onset of fibrillation, but twenty-four hours later it had fallen 25 mm. Hg. and remained relatively low until about thirty-six hours after the heart had become regular once more. Then the systolic pressure rose to 185 mm. Hg, remained high for three days, and then fell to 130 the day before fibrillation again set in. The blood-pressure was taken between 10:00 a. m. and 11:00 a. m. each day, and no observations were obtained immediately before and after a change in cardiac rhythm, so the day-to-day readings give no accurate indications as to changes in blood-pressure as a factor in causing changes in the cardiac mechanism. On the hypothesis that the high blood-pressure might be a factor in maintaining fibrillation, however, the patient inhaled 0.2 c.c. of amyl nitrite about three hours after the onset of fibrillation on March 23, at which time the systolic blood-pressure was 180 mm. Hg. He became nervous and dizzy, but except for the initial rapidity the heart beat did

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[3] Lewis: Auricular Fibrillation and Its Relation to Clinical Irregularities of the Heart, Heart, 1909-10, i, 306.

[4] Lewis: Fibrillation of the Auricles; Its Effects Upon the Circulation, Jour. Exper. Med., 1912, xvi, 395.

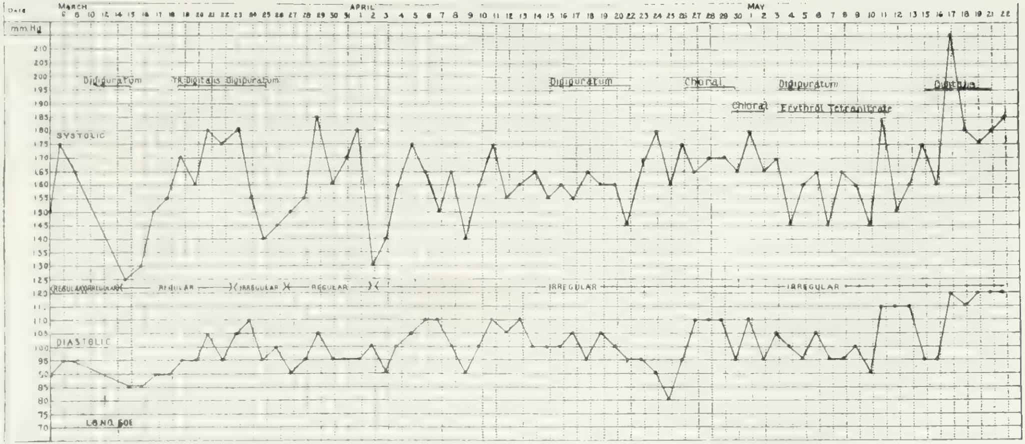

Fig. 3.—The systolic (upper line) and the diastolic (lower line) blood-pressure. The type of cardiac activity and the drug administration are also indicated.

not change, and the blood-pressure was apparently not lowered. On another occasion (April 22), three weeks after the onset of fibrillation, the systolic pressure fell during the operation of blood-letting to 115 mm. Hg without any change in the cardiac mechanism. Erythrol tetranitrate and chloral were also administered during fibrillation, but without affecting appreciably the blood-pressure or the cardiac mechanism. On the other hand, the systolic pressure reached 215 mm. Hg on one occasion during fibrillation without any change in the beat. It may be said, therefore, that no relationship between changes in blood-pressure and changes in the cardiac mechanism can be made out. The blood-pressure varied greatly, both during auricular fibrillation and during the normal rhythm, but the blood-pressure was maintained generally at a high lever, regardless of the form of cardiac activity present. These blood-pressure observations are in accord with those made by Lewis[4] on the experimental animal, in which he found that the onset of fibrillation was usually accompanied by a fall of blood-pressure, but the effect was inconstant. The circulation tended to accommodate itself to altered conditions, and to return to the same blood-pressure as that observed before the onset of fibrillation.

The effect of pressure on the neck over each vagus nerve was recorded by electrocardiograms several times, both during the normal rhythm and during fibrillation (Figs. 4-7). The abnormal susceptibility of the heart to mechanical stimulation of the vagi was striking. The length of time pressure was made over each nerve and the length of the responding pause may be tabulated as follows:

AURICULAR FIBRILLATION (FIGS. 3 AND 4)

	Pressure Over Right Vagus Seconds		Ventricular Stoppage Seconds	Pressure Over Left Vagus Seconds		Ventricular Stoppage Seconds
	3.0		3.3	3.4		4.8
	3.4		4.0	3.1		4.0
	2.8		4.0	3.6		4.4
	3.0		3.1	...		...
	3.0		3.4	...		...
Avearage.....	3.04		3.56	3.37		4.42
Proportion....	1	:	1.17	1	:	1.22

NORMAL BEAT (FIGS. 5 AND 6)

	Pressure Over Right Vagus Seconds		Ventricular Stoppage Seconds	Pressure Over Left Vagus Seconds		Ventricular Stoppage Seconds
	1.4		3.2	2.0		3.6
	1.9		3.0	2.0		4.0
	1.9		3.0	2.0		1.9
Avearage.....	1.73		3.06	2.0		3.17
Proportion....	1	:	1.77	1	:	1.53

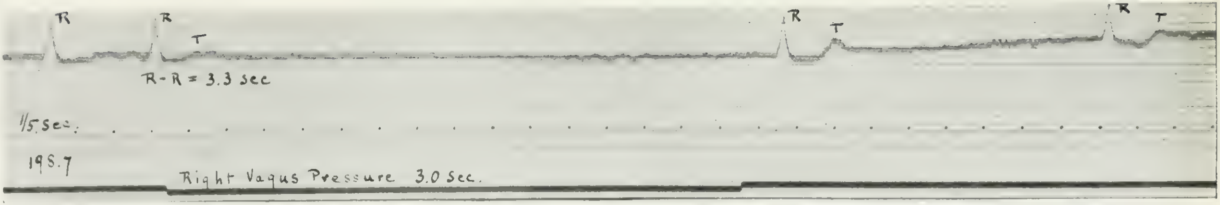

Fig. 4.—Curve 198.7. February 28. The effect of pressure for three secondsover the right vagus during auricular fibrillation.

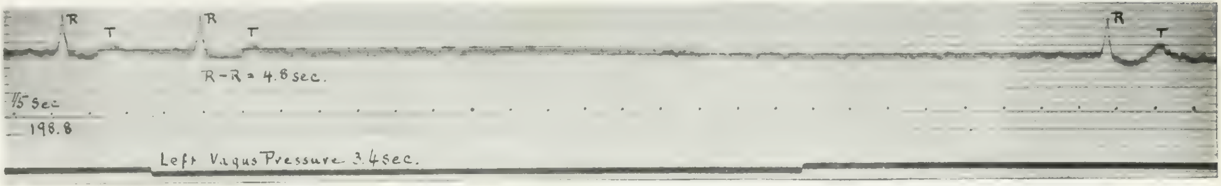

Fig. 5.—Curve 198.8. February 28. The effect of pressure for 3.4 seconds over the left vagus during auricular fibrillation.

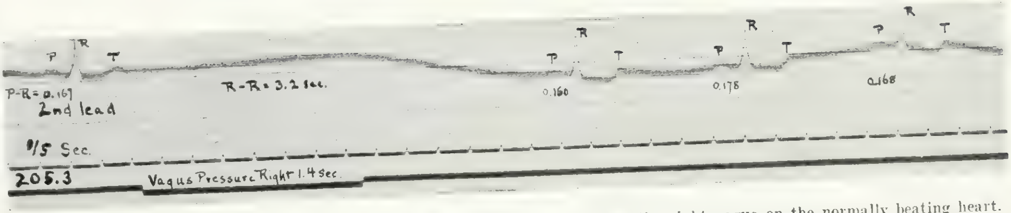

Fig. 6.—Curve 205.3. March 4. The effect of pressure for 1.4 seconds over the right vagus on the normally beating heart.

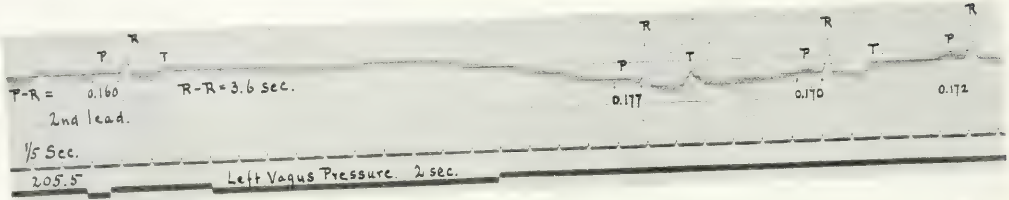

Fig. 7.—Curve 205.5. March 4. The effect of pressure for 2 seconds over the left vagus on the normally beating heart.

Thus it is seen that neither during auricular fibrillation nor during the normal beat can any definite difference be made out between the effects of right and left vagus pressure, such as can sometimes be demonstrated in man (Robinson and Draper[5]), and as can be almost constantly shown with faradic stimulation of the nerves in the dog (Cohn,[6] Robinson[7]). The ventricles were stopped for a longer time proportional to the length of pressure when the heart was beating normally than when auricular fibrillation was present, whether the left or the right nerve was pressed on.

The mechanism responsible for the ventricular pauses which followed vagus pressure during auricular fibrillation is apparently different from that which brings about the stoppage of the normally beating heart. The electrocardiograms indicate that the activity of the fibrillating auricles was unaffected by pressure over the vagi, while they show that the normally beating auricles were brought to rest by this procedure. The manner by which vagus pressure brings about the long cessation in the ventricular activity in cases of auricular fibrillation has been discussed by Robinson and Draper,[5] and it was concluded that the ventricular pauses are apparently due to the blocking of stimuli from the auricles. There was no evidence as to whether this striking effect depends on an increased susceptibility of the conducting fibers to vagus stimulation or whether it depends on the stimuli from the fibrillating auricles being of such a nature that only slight lowering of the conductivity succeeds in blocking them. The possibility must also be considered of some quantitative change in the auricular activity which is not to be detected in the electrocardiograms, but which makes it incapable of stimulating ventricular contractions.

When the heart was beating normally there is practically no evidence that pressure over either vagus nerve lowered the conductivity, as the P-R time was never prolonged beyond 0.21 second after the cardiac stoppage in any of the records. The marked effect on the rate of the whole heart is in sharp contrast to the effect on conduction. It may be, however, that this effect on rate is responsible for the lack of effect on conduction, for during the cardiac standstill the conductivity of the heart is freed from the influence of functional fatigue, and so has its normal capabilities at the end of the cardiac pause. The harmonizing of the effects of vagus pressure on the heart during auricular fibrillation with that observed when the heart was beating normally is difficult.

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[5] Robinson and Draper: I. Studies with the Electrocardiograph on the Action of the Vagus Nerve on the Human Heart, Jour. Exper. Med., 1911, xiv, 217; II. Studies with the Electrocardiograph on the Action of the Vagus Nerve on the Human Heart, Jour. Exper. Med., 1912, xv, 14.

[6] Cohn: Jour. Exper. Med., 1912, xvi, 732.

[7] Robinson: The Influence of the Vagus Nerves on the Faradized Auricles in the Dog's Heart, Jour. Exper. Med., 1913, xvii, 429.

The marked susceptibility of the heart to mechanical stimulation of the vagi may have been another expression of the cardiac abnormality which caused the auricular fibrillation. The hearts of patients with auricular fibrillation are often markedly affected by pressure over the vagi and an abnormal response to this procedure by a normally beating heart may possibly indicate that auricular fibrillation is more likely to occur in it than in a heart less affected by vagus pressure. It is difficult to say whether this abnormal response indicates a so-called heightened "vagus tone" or whether the heart itself is responsible for the marked response. A series of experiments were undertaken with the hope primarily that some new light might be thrown on the question of the relation of vagus activity and auricular fibrillation, but the results of the experiments[7] do not afford any positive evidence as to the rôle the vagi may play as a causative factor of auricular fibrillation in man. The dog's auricles may be thrown into fibrillation and tachycardia by direct faradization as readily after the vagi are cut as before, but vagus stimulation holds the auricles in their abnormal state of activity after it has been once set up by faradization.

The effect of atropin in our case was observed only during fibrillation, and after 0.9 mg. atropin had been given hypodermically the ventricular rate increased markedly from 84 to 158 beats per minute, recorded by an electrocardiogram taken forty minutes after the administration of atropin. The waves of fibrillation were not so distinct in the records obtained during the rapid ventricular rate as before. The great increase in ventricular rate following atropin indicates that the vagi were constantly strongly active at this time in controlling the ventricular rate. A desire not to disturb the normally beating heart prevented the use of atropin during the periods of regular rhythm.

A series of electrocardiograms were made directly from various points on the chest wall during the normal beat and during fibrillation. The technic described by Lewis[8] was followed, in the hope of gathering further evidence regarding the significance of the waves of auricular fibrillation in the electrocardiograms. The results were unsatisfactory, as neither the P waves nor the waves of auricular fibrillation were distinct.

When this patient is considered from an anatomical rather than from a physiological viewpoint, it is found that the heart is normal as regards its size, position and the character of the heart sounds. No valvular murmurs were ever heard, and although the second aortic sound was somewhat accentuated, the muscle sounds were of good quality. The outline of cardiac dulness was measured repeatedly, and no changes in size as those observed by Lewis and Schleiter[9] could be made out, as an accompaniment of the changes in mechanism. A slight increase in the size of the heart between the time of admission and of discharge was noted, however, the total width increasing 1 cm. during this time.

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[8] Lewis: The Origin of the Electric Oscillations and the Direction of Contraction of the Ventricle in Instances of Complete Irregularity of the Heart (Auricular Fibrillation), Quart. Jour. Med., 1911, v, 11.

The constantly high blood-pressure and the palpable arteries in the arms and temporal regions led to the diagnosis of arterial sclerosis. The urine gave no evidence of diseased kidneys, as the usual tests were repeatedly negative except for several hyaline casts on two occasions. The functional activity of the kidneys was tested May 7 by the technic of Rowntree and Geraghty,[10] 6 mg. of phenolsulphonephthalein being injected intramuscularly. The first appearance of the drug in the urine was not definitely determined, but was estimated at about ten minutes. During the first hour 36.8 per cent. and during the second hour 21.9 per cent., or a total for two hours of 58.7 per cent. of the drug was excreted. Thus the functional activity of the kidneys was but slightly below the normal limits of excretion (40-60 per cent. the first hour, and 60-85 per cent. in two hours). The sole definite anatomical lesion, therefore, is apparently arterial sclerosis.

Arterial sclerosis is frequently a prominent characteristic of cases of auricular fibrillation. Thus Lea[11] found it present in 57.1 per cent. of the non-rheumatic cases in his series. No definite change in the cardiac muscle has been described in these cases with sufficient frequency to allow any conclusions to be drawn as to an anatomical basis for auricular fibrillation, and the post mortem examinations of some of the hearts in which fibrillation had been present reveal hearts which are anatomically sound (Gossage and Hicks[12]). Lewis[3] believes that it is changes in the walls of the auricles themselves which probably cause fibrillation, and he has expressed the opinion that anemia of the auricular walls may be a factor in setting up fibrillation. Changes in the blood-supply of the auricular walls may well have been an important factor in causing the attacks of fibrillation in our patient. The evident arterial sclerosis and the high but markedly changing blood-pressure might readily have caused abnormalities in the cardiac blood-supply, which not only rendered the auricles more prone to fibrillation and abnormally susceptible to vagus stimulation, but also furnished the immediate cause of an attack of auricular fibrillation by a temporary diminution of the cardiac circulation. There is very little in support of this hypothesis, but arterial sclerosis and high blood-pressure have been prominent in several cases of transitory auricular fibrillation which have been observed. Thus Hornung[13] reports three cases in which these abnormalities were prominent features, and arterial sclerosis was also mentioned in two of Fox's[14] six cases. The case reported by Lewis and Schleiter, although only 28 years old, had somewhat thickened arteries, but on the one occasion recorded the blood-pressure was low.

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[9] Lewis and Schleiter: The Relation of Regular Tachycardias of Auricular Origin to Auricular Fibrillation, Heart, 1912, iii, 173.

[10] Rowntree and Geraghty: An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonephthalein, Jour. Pharm. and Exper. Ther., 1909-10, i, 579.

[11] Lea: Some Points in Relation to the Etiogoly of Auricular Fibrillation, Quart. Jour. Med., 1911, iv, 423.

[12] Gossage and Hicks: On Auricular Fibrillation, Quart. Jour. Med., 1913, vi, 435.

The paroxysms of auricular fibrillation may occur over a period of many years, and our patient had them apparently for twelve years. One of Hornung's cases suffered with attacks of cardiac arhythmia for five years and another for at least ten, while one of the cases reported by Fox, the case originally observed by Cushing and Edmunds, had attacks for over twenty years. These cases, therefore, do not always deserve the bad prognosis which is usually accorded to auricular fibrillation. They may have anatomically normal hearts and be closely allied to cases of paroxysmal tachycardia, as Lewis and Schleiter point out. The prognosis may not necessarily be more grave than in tachycardia. However, the auricular fibrillation tends to become permanent, as Fox's cases well illustrate, and this is what happened in our case, as fibrillation was present during the last two months that he was in the hospital, and continued until his death about two months after his discharge. There is, therefore, apparently a group of cases which may be termed paroxysmal auricular fibrillation, in which arterial sclerosis may be an underlying cause of the abnormal cardiac activity, and in which attacks of fibrillation may recur over a period of many years in patients with anatomically normal hearts, without great impairment to the general health.

SUMMARY

A case is reported in which transient attacks of auricular fibrillation were observed and recorded by electrocardiograms. These attacks had apparently occurred over a period of twelve years, and auricular fibrillation became permanent while under observation. No definite cause could be discovered as initiating the attacks. No definite relation could be established between changes in blood-pressure, which was always abnormally high and variable, and the changes in the cardiac mechanism. The heart was strikingly susceptible to pressure over each vagus nerve, both during fibrillation and during the normal cardiac activity. This abnormality may be another expression of the changes causing auricular fibrillation. Electrocardiographic records of these vagus effects were obtained.

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[13] Hornung: Über atypische Tachykardische Paroxysmen, Deutsch. Arch. f. klin. Med., 1907, xci, 469.

[14] Fox: The Clinical Significance of Transitory Delirium Cordis, Am. Jour. Med. Sc., 1910, cxl, 815.

The heart of the patient gave no signs of an anatomical lesion, but arterial sclerosis, a frequent accompaniment of auricular fibrillation, was present. The presence of this lesion and the high, inconstant blood-pressure suggest the possibility that changes in the cardiac blood-supply may have been the underlying causative factor in this case. Other cases showing attacks of auricular fibrillation occurring over a period of years have been reported in which high blood-pressure and arterial sclerosis were prominent features. These cases seem closely allied to paroxysmal tachycardia, and although the auricular fibrillation tends to become permanent, the prognosis for them is not necessarily so grave as that which is given in ordinary cases of auricular fibrillation with outspoken cardiac lesions.

1806 Locust Street.

THE MUTUAL ACTION OF CERTAIN DIGESTIVE FERMENTS *

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In the earliest days of the investigation of some of the important soluble ferments, or enzymes, the question of their behavior toward each other came up for study. In the human body we have to consider the action of the salivary, the gastric, the pancreatic and the intestinal ferments, and the behavior of each one of these may be modified not only by the reaction of the medium in which it acts, but also by the presence of others. Since the activity of the salivary diastase is not confined to the mouth, but is continued to the stomach, the effect of the hydrochloric acid and pepsin present has naturally been the subject of frequent studies. Practically, the behavior of the acid alone has real importance, since the ptyalin is so sensitive to the acid that even minute traces are sufficient to render it inert. That pepsin, also, may have an effect on ptyalin, or ptyalin on pepsin, are academic questions of little practical importance, and of no importance at all in the present inquiry.

Much more importance attaches to the inquiry, What is the action of the gastric juice, that is, of pepsin plus hydrochloric acid, on the group of ferments furnished by the pancreatic secretion? In the normal conditions obtaining in the animal body, and especially in the human body, it is evident that there is no interference of the one with the other. Passing down into the intestine remains of the gastric secretion, with acid reaction, become speedily neutralized and brought into a condition in which pepsin, if any of it remains, cannot act on either proteins or ferments. The question, however, becomes a very different one when we seek to determine the action of the pepsin, or the whole gastric juice, on artificial pancreas products given by the mouth, and which therefore must pass through the stomach.

This is the question which comes up in studying the behavior of the commercial product known as pancreatin, and we are permitted to ask about the action of these pancreas ferments, on the one hand, on pepsin, and, on the other hand, of the action of pepsin on them. The question is an old one and has been in the literature many years. We find that in his classic researches on the preparation and properties of trypsin Kühne, in the seventies of the last century, touched on it, and many subsequent investigators have dealt with some phase of it.

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In view of the wide-spread use of pancreatin the inquiry has no little practical importance, and it comes to us now through questions raised in the investigations of the Council on Pharmacy and Chemistry on pancreas preparations which are supposed to resist the action of the gastric juice and exhibit their characteristic effects after passing through the stomach.

That "pancreatin" is much weakened in its action by contact with pepsin is often affirmed and perhaps generally believed, if one can judge by the somewhat vague statement of the Pharmacopeia, Eighth Revision: "The digestive power of pancreatin is injured by contact with pepsin in solution." Not only is this statement vague, but also it may not be altogether in accord with facts. The vagueness, however, is in a measure associated with the vagueness in the definition of pancreatin itself. Under the name "pancreatin" we understand a product obtained in some manner from the pancreas of the hog or ox, but as to the method of preparation or the ferment content of the article there is not much agreement. It is usually assumed that all the pancreas enzymes are present, but in the method of testing official in our Pharmacopeia only one of them is practically recognized and the content of this is assumed to be small. As to whether the determined value found for the amylopsin is to be taken as a measure of the content of the other ferments, or not, nothing is said.

What is called pancreatin is often not much more than fat-free ground pancreas. Perhaps this is usually the case, but in the older view, and that still held by many writers, pancreatin should be obtained by some process of *extraction* from the pancreas, and precipitation or concentration of the extract. The question of expense seems to prevent the manufacture in this way, as a rule, and there would be little or no advantage in the matter of stability.

Pancreas powders, or extracts, are in general very low in the lipase enzyme, and in the laboratory as well as in the manufacturing scale it is difficult to secure a permanent product which has much fat-splitting power. In dealing with "pancreatins," or other commercial products of this class, we are practically concerned with their amylolytic or proteolytic power only. To what extent, if at all, are these ferment activities injured by contact with gastric juice or its pepsin-acid equivalent? And in turn, have these ferments any action on pepsin?

These are the questions we have attempted to answer through a series of experiments.

1. THE ACTION OF HYDROCHLORIC ACID AND PEPSIN ON AMYLOPSIN

This is the statement of a problem which is more ideal than practically workable, since neither the amylopsin nor the pepsin is obtainable in a pure or nearly pure condition. Both of the ferments, as we obtain them commercially, or as we prepare them in the laboratory, are associated with relatively large amounts of matter which, while inert as far as ferment action is concerned, may be very important in modifying ferment action. This is true of the phosphate and other salt content of the ferment products.

For the purposes of this inquiry the question is asked what is the behavior of the best obtainable laboratory or commercial products toward each other? and that is the problem to be discussed.

It requires but a brief study to show that the starch-converting ferment from the pancreas, as well as that from malt, is very sensitive toward acids.

Before touching the question of the pepsin behavior, it is therefore necessary to fix the limits of the acid action, as this, rather than pepsin, may be the main factor in the case. The Pharmacopeial statement is misleading in this respect. Various statements are found in the literature concerning the acid concentration which stops the amylolytic action of the ferments,[1] and these statements are often in conflict because the experiments on which they were based were doubtless made with products of very different degrees of purity, especially in respect to salt content. The phosphates of sodium, potassium, calcium and magnesium which are associated to some extent with most of these ferment products are important factors in modifying the action of added hydrochloric acid, and it must not be forgotten that the binding power of protein for acid is another factor.

To eliminate these factors as far as possible we have sought to find the behavior of the acid by using glycerol extracts of the ferment, as well as a considerable number of dry products.

These points, then, are to be considered under the general topic of pepsin-hydrochloric acid-amylopsin action:

A. Action of dilute acid on glycerol extracts and dry products from the pancreas.

B. Possible action of pepsin, alone, on these products.

C. Action of pepsin and acid on the same products.

The discussion of these problems must be preceded by an explanation of the methods of investigation employed, which, for the present purpose, need be but brief.

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[1] See, for example, the quotations in the work of Green, The Soluble Ferments and Fermentation, and the work of Oppenheim, Die Fermente und ihre Wirkungen; also Effront, Die Diastasen.

A. ACTION OF ACID ON GLYCEROL EXTRACTS

General Conditions

Glycerol extracts of the pancreas have been used by many observers, and in our own laboratory for years. The activity of such extracts and the best conditions for preparation have been most clearly pointed out by Vernon in a series of papers which have gone pretty fully into this phase of the subject.[2]

In our work the pancreas extracts were made by mincing the organs very fine and macerating through about three weeks with twice their weight of pure glycerol. The mass, thick at first, grew much thinner in time from the evident partial digestion. Finally the liquid was separated pretty thoroughly from the suspended particles by straining and by centrifugalization in a powerful machine capable of taking eight tubes of 100 c.c. each at one operation. In this way we secured about 1,600 c.c. of a cloudy liquid which deposited but little on standing. This was extremely active in amylopsin and trypsin, although prepared with careful exclusion from contact with any portions of the intestinal mucosa. Even without the addition of salt the liquid was markedly active on starch, but the addition of the salt brought an increase in the activity. In all our experiments aqueous dilutions of this extract were used, in some cases a 1:10 dilution, and in other experiments a 1:50 dilution, filtered.

Vernon and others who have worked with such extracts state that they retain their activity through months. With water solutions, however, the case is quite different, and in a 1:50 dilution, or even in a 1:10 dilution there may be a very marked loss of activity in from ten to fifteen hours, as when the solutions are allowed to stand over night. The loss of power is much increased by a slight elevation of temperature and at 40 C. may be very decided.

If, however, the dilutions are made with salt water in place of pure water, the stability is found to be much greater. These facts were illustrated by a large number of experiments made with some commercial pancreatin preparations, as well as with glycerol extracts, in an effort to find an explanation for the great variability in the relative strengths of the market preparations. It was found necessary, therefore, to use the water solutions of glycerol extracts as soon as possible after preparation in order to secure the maximum activity. This precaution is recommended by several manufacturing firms in methods given for testing their pancreatins.

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[2] Vernon, H. M.: These papers deal with tryptic as well as diastatic action. See Journal of Physiology, 1901, xxvi, 405; 1901, xxvii, 269, 316, and in other places.

The value of diastase preparations is practically determined by their action on starch paste. To secure definite and constant results much depends on the method employed in making the paste, and for details on this point we refer to the general scheme as followed in this laboratory and described by Johnson and one of us[3] in a recent publication.

Method of Observation

In following out the action of diastases on clear starch paste made up usually to the strength of 10 gm. of anhydrous starch to the liter, we employ the form of the iodin test worked out in this laboratory and reported by Johnson.[4] In the digestions, always at 40 C., we carry the reaction to the colorless end-point, when 5 drops of the digesting fluid are added to 5 c.c. of a dilute iodin solution, made by dissolving 1 gm. of iodin and 2 gm. of potassium iodid in 125 c.c. of water and diluting 2 c.c. of this solution to 1 liter, finally, for use.

When the dilute starch paste is added to this iodin solution the blue color comes out sharply. As digestion proceeds the blue changes to a purple tint, then a purplish red, a rather deep red, a light red or reddish, a yellowish shade and finally colorless, or at most the faint shade of the weak iodin solution. It may be advantageous to use even a weaker iodin to note the final tint, but usually we do not do this. When used with pancreatic preparations Sherman[5] objects to this method of following the reaction because of the appearance of the red shades. But it is just this appearance and the gradual changes which constitute the most desirable features of the iodin test. Its advantages have been pointed out by others.[6] The conversion of starch to sugar is far from being an immediate process, and whether the dextrins are definite and sharply definable bodies or not, we must admit that there are various stages in the change from the original starch to the final malt sugar. The purple color which succeeds the blue corresponds to the so-called amylodextrin of some authors, and its appearance is a valuable indication of the progress of the action. This stage is followed by that of other mixtures, not definite, of course, but all clearly suggesting the rapidity of the transformation. It is desirable to employ a method in which this transformation may be conveniently followed, and this is true of the iodin method as used by us. At the end we have just as much information as may be derived from the copper reduction tests, which we have often used for controls, and much additional information, besides, which may be lost by making the copper reduction tests in the presence of an excess of starch. In technical inquiries as to the value of relatively strong diastase preparations the copper methods are undoubtedly the most satisfactory, but in a strictly physiological study, where the time element is important, certain advantages seem to rest with the iodin process.

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[3] Long and Johnson: Jour. Am. Chem. Soc., 1913, xxxv, 896.

[4] Johnson: Jour. Am. Chem. Soc., 1908, xxx, 798.

[5] Sherman and Colleagues: Jour. Am. Chem. Soc., 1910, xxxii, 1081.

[6] See Roberts: Proc. Royal Soc., 1881, xxxii, 145; Detmer: Ztschr. f. physiol. Chem., 1882, vii, 1.

With this general discussion of the preparation of the materials and the method of testing we are ready for a description of the experiments carried out to test the behavior of weak acids toward the starch-amylopsin reaction.

Like the other actions, that of acids on the starch-digesting ferment of the pancreas has been much discussed. It seems desirable to bring out certain conditions here which have not been clearly recognized, although they have been in part pointed out by previous writers.

Amylopsin is much more sensitive to the action of traces of acids than to alkalies, and the final effect is more or less dependent on the presence of salts, which may not only serve to stimulate the catalytic action of the ferment, but also act to depress the activity of the acid hydrogen in its paralyzing behavior. Attempts have been made to show that diastase absorbs gaseous hydrochloric acid through some other than a basic property, and that a large part of the gas may be removed by suction without having fully destroyed the ferment. Panzer[7] has published a lengthy investigation on this subject, but the weight of acid added to the ferment preparations was in all cases so large as to permit no conclusion concerning the behavior of the small acidities which really come into consideration where the physiological action is concerned. The same is true of the experiments where aqueous acid was used with gram or half-gram weights of the ferment. In one case 1 gm. of a certain diastase preparation and 0.06775 gm. of hydrochloric acid, made up to about 80 c.c., stood an hour and was then neutralized with sodium hydroxid and diluted to 100 c.c. Portions of this dilution were then allowed to act on starch paste, the iodin and sugar tests being made from time to time. The figures given show a greatly diminished diastatic conversion, as one might expect from the rather high acid concentration. In discussing this and other experiments, the author states that the small amount of salt formed in the neutralization cannot be in any way responsible for the modification of the diastatic action, since such small quantities are of no significance. This conclusion does not appear to be warranted by facts already referred to, which will be brought out below. The salt here is undoubtedly of very considerable importance.

In our tests we considered the behavior of those small weights of acid which have practical significance. Small definite volumes of the glycerol extracts, diluted, were mixed with known weights of acid, and the mixtures made to constant volumes. These were then incubated at 40 C. through a period of half an hour, usually, after which a constant volume of the 1 per cent. starch paste was added and the incubation continued. From time to time drops were taken from the incubating mixtures to test for the disappearance of the iodin-starch reaction which would show the conversion of the starch to sugar or forms of dextrin which do not react with iodin. The rapidity of this conversion is a measure of the activity of the amylopsin present. As the action of the acid becomes evident, the time required to convert all the starch to products not giving a color with iodin is lengthened.

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[7] Panzer: Ztschr. f. physiol. Chem., 1912, lxxxii, 276.

Two conditions in the last steps of the reaction may be noticed. After the incubation of the ferment and acid mixture the starch may be added directly and a new incubation made, or, after the preliminary incubation, a little weak alkali may be added to neutralize the acid before mixing with the starch paste. In the first case the starch digestion takes place in a slightly acid medium, while in the second it is neutral. Both lines of observation were followed.

In all cases some salt was added to the amylopsin extracts, to bring them all up to the degree of maximum activity which may be secured in this. The importance of this in comparative tests has been frequently pointed out.

Experiment 1.—Ten c.c. of a glycerol extract of pancreas made by diluting the original thick extract with water in the proportion of 1 : 49. One hundred mg. of sodium chlorid added. Amounts of hydrochloric acid as shown below were added from dilute solution and the whole diluted to 50 c.c. for each test, carried out in 200 c.c. flasks. Incubated thirty minutes at 40 C. and added to each mixture 50 c.c. of 1 per cent. starch paste. Incubated again and withdrew, from time to time, 5 drops from each flask for iodin tests.

In a control flask no acid was used, and tests made with this at the end of three minutes showed complete absence of color, indicating total conversion of the starch. In five other flasks, with 1, 3, 5, 7 and 9 mg. of acid there was no perceptible conversion, as a strong iodin reaction was found in each case, even after an hour of incubation with the starch. In a parallel experiment the acid, after the preliminary incubation of thirty minutes, was neutralized with sodium bicarbonate. In the following incubation with starch paste the same results were obtained as before.

Experiment 2.—Ten c.c. of a 1 : 10 dilution of the glycerol extract were taken for each test and with 100 mg. of salt diluted to 50 c.c. Each test flask contains, then, in the 50 c.c. 1 c.c. of the original glycerol extract, and weights of acid as in Experiment 1. After thirty minutes incubation at 40 C. 50 c.c. of 1 per cent. starch paste was added to each flask and final incubation began. In the control flask, with no acid added, the starch reaction disappeared in three minutes. In a flask with 1 mg. of hydrochloric acid the starch reaction began to fade in less than six minutes, was weak in ten minutes, and absent in an hour. With stronger acid concentrations, 3 mg. and above, the starch reaction was always sharp, even after one hour.

Experiment 3.—Conditions same as in 2, but twice as much of the glycerol extract present. In the flask with 1 mg. of acid present the starch reaction disappeared in the same manner as before, but with the concentrations of 3, 5, 7 and 9 mg. of hydrochloric acid there was a perceptible change in the starch reaction in an hour. The blue color had given place to purple.

In this last experiment there is a suggestion that with larger initial amounts of the pancreas ferment present there is greater practical resistance to the acid. Some of the ferment seems to have escaped destruction and is able to bring about a slow conversion of starch. In the following experiment still more of the ferment was used.

Experiment 4.—For each test 5 c.c. portions of the original glycerol extract were diluted with water to 50 c.c., receiving at the same time weights of acid as given in Table 1 and 100 mg. of salt in each case. After the preliminary incubation of thirty minutes at 40 C., 50 c.c. of paste was added to each flask and the final incubation started. The results are shown in Table 1. Complete destruction of the starch, as shown by absence of iodin reaction, is indicated by +; when there is no conversion of starch this in indicated by —. Partial conversion is indicated by ∓, with this sign to indicate a progressive change →+.

TABLE 1.—Digestion of Starch with Pancreas Extract Previously Incubated with Hydrochloric Acid and Salt. (Experiment 4)

	Time of Incubation, Minutes					
HCl Mg.	3	6	10	15	30	45
0	+	+	+	+	+	+
1	+	+	+	+	+	+
3	+	+	+	+	+	+
5	+	+	+	+	+	+
7	∓	+	+	+	+	+
9	∓	→+	+	+	+	+
11	∓	→+	→+	→+	→+	→+

With this stronger concentration of enzyme, its destruction appears to be very much delayed. The results seem to suggest that the effect depends not only on the acid concentration, but on the enzyme concentration also. In other words, a given weight of acid will destroy or inhibit the action of a given amount of enzyme only. A weight combination between the two is suggested in this way, but there is another possibility which must be noticed, and that is that the increasing weight of inert protein substance added with the largest weights of ferment binds to some extent the acid and weakens its action.

The amount of protein present, however, is in no case sufficient to hold enough of the acid to effect a marked change in its concentration. Certain salts present may have a larger influence on the behavior, as will be pointed out below.

A moment's consideration will suggest that the absence of digestive power on the part of the ferment, as shown by the starch test made, may be explained in two ways: first, the ferment may be destroyed in the incubation process, or second, the ferment may not be destroyed, but its activity toward the starch may be hindered by the presence of the acid. It is well known that larger quantities of acid will stop conversion of the starch, and possibly with the smaller quantities here employed this may take place, without involving the actual destruction of the enzyme. Some experiments with an active commercial pancreatic diastase throw light on this point. This product contains considerable chlorid, from the process of manufacture.

Experiment 5.—Pancreas powder, 500 mg. to 100 c.c. plus 3 mg. of hydrochloric acid. Incubated 50 c.c., *a*, through thirty minutes at 40 C., and allowed the other 50 c.c. *b*, to stand thirty minutes at room temperature. Then mixed small volumes with 50 c.c. of starch paste, 1 per cent., incubated again, and tested after the intervals as shown in Table 2. The degree of conversion is indicated as in 4.

Exepriment 6.—Conditions same as in 5, but 6 mg. of hydrochloric acid was present in the 100 c.c. with the 500 mg. of pancreas powder (Table 3).

Experiment 7.—Conditions as in 5 and 6, but 12 mg. of hydrochloric acid present in the 100 c.c. for the preliminary incubation (Table 4.)

TABLE 2.—Digestion of Starch with Pancreas Extract Previously Incubated with 3 Mg. Hydrochloric Acid. (Experiment 5)

Ferment Solution c.c.	Time of Action on Starch, Minutes						
	a					*b*	
	5	10	20	40	60	5	10
4	—	→+	→+	+	+	+	+
6	—	→+	→+	+	+	+	+
8	—	+	+	+	+	+	+
10	—	+	+	+	+	+	+

TABLE 3.—Digestion of Starch with Pancreas Extract Previously Incubated with 6 Mg. Hydrochloric Acid. (Experiment 6)

Ferment Solution c.c.	Time of Action on Starch, Minutes							
	a					*b*		
	5	10	15	25	35	5	10	15
4	—	—	—	—	—	→+	+	+
6	—	—	—	—	—	+	+	+
8	—	—	—	—	—	+	+	+
10	—	—	—	—	—	+	+	+

TABLE 4.—Digestion of Starch with Pancreas Extract Previously Incubated with 12 Mg. Hydrochloric Acid. (Experiment 7)

Ferment Solution c.c.	Time of Action on Starch, Minutes							
	a					*b*		
	5	10	15	25	35	5	10	15
4	—	—	—	—	—	→+	+	+
6	—	—	—	—	—	+	+	+
8	—	—	—	—	—	+	+	+
10	—	—	—	—	—	+	+	+

With the smallest acid concentration, 3 mg. of hydrochloric acid to 100 c.c., it is seen that the preliminary incubation does not completely destroy the ferment action. It is somewhat delayed, however. Possibly, the action of the acid is much modified by the protein and salts present. But with 6 and 12 mg. of acid to the hundred cubic centimeters, with the 500 mg. of pancreas powder there is a very different picture. In the incubated portion there appears to be a complete destruction of the enzyme, since no change is found in the reaction with starch paste with the largest amount of ferment solution or after prolonged action on the starch. In the portions not incubated, with the acidity the same, starch conversion goes on rapidly in all cases.

These experiments show that the amounts of acid used, which are sufficient to destroy the ferment in incubation, are not sufficient to impede the actual digestion.

The acid effect is shown in the incubation with the diastase, not in the behavior of the diastase with starch. Other experiments showed that starch conversion will go on in presence of much larger weights if acid, but it is evident that very small concentrations of acids destroy the ferment at the incubation temperature.

In this connection it may be asked what is the effect of the addition of alkali soon after the addition of acid to the ferment? In the experiments of Panzer, referred to, an attempt was made to answer this question, but the somewhat unfavorable conditions of the experiments made the answer uncertain. Some of our experiments on this point suggested a partial recovery of activity, by speedy addition of alkali. In mixtures incubated for some time the addition of alkali had but little effect, but when sodium bicarbonate was added soon after the acid, with no incubation, the result was somewhat different, as shown by these experiments.

EXPERIMENT 8.—Ten c.c. portions of a 1 : 10 glycerol extract of pancreas (1 c.c. of the original strong extract diluted to 10 c.c. with water) was mixed with 100 mg. of salt and acid as below and diluted to 50 c.c. No preliminary incubation. Each portion was then incubated with 50 c.c. of 1 per cent. starch paste for the time shown in Table 5.

TABLE 5.—DIGESTION OF STARCH WITH PANCREAS EXTRACT MIXED WITH SALT AND HYDROCHLORIC ACID. (EXPERIMENT 8)

	Time of Action on Starch, Minutes					
HCl Mg.	3	6	10	15	30	90
0	+	+	+	+	+	+
1	+	+	+	+	+	+
3	—	—	—	—	—	—
5	—	—	—	—	—	—
7	—	—	—	—	—	—
9	—	—	—	—	—	—

EXPERIMENT 9.—Conditions as in 8. But immediately after mixing with the acid and shaking, the equivalent weights of sodium bicarbonate were added. That is, the acid was neutralized as quickly as possible, so that its action on the ferment solution was for a brief time only. Then each portion was mixed with the starch paste and incubated as before (Table 6).

TABLE 6.—DIGESTION OF STARCH WITH PANCREAS EXTRACT, MIXED WITH SALT AND HYDROCHLORIC ACID, NEUTRALIZED WITH SODIUM BICARBONATE. (EXPERIMENT 9)

	Time of Action on Starch, Minutes					
HCl Mg.	3	6	10	15	30	60
0	+	+	+	+	+	+
1	+	+	+	+	+	+
3	→+	+	+	+	+	+
5	—	—	→+	→+	→+	→+
7	—	—	—	—	—	—
9	—	—	—	—	—	—

With the weights of acid here used there seems to be a practical destruction of the ferment in a minute or less, of action. The failure to convert the starch is not due to the presence of acid, since in Experiment 9 the acid is neutralized before ferment solution and paste are mixed. The reaction here is neutral. It will be noticed that with the smaller acid concentration there is some little effect by speedy addition of the bicarbonate, but it is not very marked. Unless protected by protein or salts the ferment is very rapidly injured or destroyed by traces of acid.

There appears, at first sight, to be a discrepancy between the last results and those of Experiment 7, in which 12 mg. of acid with ferment diluted to 100 c.c., but not incubated, left the diastatic activity still marked. In this case, however, the ferment was in the form of 500 mg. of a pancreas powder, and the effect of the protein and salts present would doubtless be of moment. The glycerol extracts do not contain much protein.

From all these experiments it appears that very low concentrations of acid destroy amylopsin. Experiment 8 shows that 3 mg. of the acid, not neutralized at once, destroys the diastase activity to such an extent that there is practically no starch conversion in ninety minutes. This is a strength of 0.006 per cent. in the ferment solution, before adding the starch. That is, 1.6 c.c. of 0.1 normal hydrochloric acid to 100 c.c. destroys even the beginning of starch conversion. Kendall and Sherman[8] have shown that about one-fourth of this stops the conversion to the sugar stage in a diastase-starch mixture. Our results are not very different from those found by Kjeldahl for the effects of dilute sulphuric acid on malt infusions. He found that 10 mg. of the acid for 100 c.c. of paste and infusion practically prevented the starch conversion.[9]

Langley and Eves[10] state that 0.005 per cent. of hydrochloric acid is destructive to the action of ptyalin, while one-third of this slows the reaction perceptibly, which accords pretty well with our experience.

But it must be recognized that the amount of the ferment, or the accompanying proteins, plays a very important part here, as shown by Experiment 4, in which a dilution of the same glycerol extract, but five times as strong as in 2, was employed. In that experiment, even after incubation, a marked diastatic activity was found in a solution with 18 mg. hydrochloric acid to 100 c.c. of ferment solution. This fact may reconcile the somewhat conflicting statements given by Langley and Eves[10] and by Chittenden and Ely[11] for the destructive effect of the acid.

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[8] Kendall and Sherman: Jour. Am. Chem. Soc., 1910, xxxii, 1091.

[9] See Effront: Die Diastasen, 1900, p. 121.

[10] Langley and Eves: Jour. Physiology, 1883, iv, 18.

[11] Chittenden and Ely: Am. Chem. Jour., 1882, iv, 107.

Small amounts of acid are undoubtedly stimulative under certain conditions, and often by the formation of an alkali salt. Where relatively large amounts appear to have but slight action, it may be on account of the presence of much protein, which combines with the acid, or on account of salts like bicarbonates or phosphates, which in a sense neutralize it through liberation of a weaker acid of lower dissociation. It is certain that the ferment, not protected in some such manner, is extremely sensitive.

It is doubtless true that the hydrogen ion content of the solutions in question is the important factor in determining the action on the ferments. This has been shown for a number of enzymes and is probably the case here. In this connection the papers of Sörenson[12] deserve consideration. But in addition to the effect of the hydrogen ions there is also a neutral salt effect which is not so clearly understood and which complicates the general behavior.

B. THE ACTION OF PEPSIN ON AMYLOPSIN

We come now to the consideration of the behavior of pepsin alone toward the solutions of pancreatic diastase. It is commonly held that pepsin is without any action in neutral solutions or solutions of very low acidity, and this is doubtless true in respect to the behavior with coagulated egg albumin and other common protein substances. It does not *necessarily* follow that the same should hold for diastase or other enzymes. There appear to be no very definite statements on this point in the literature. Experiments reported by Wroblewski, Bednarski and Wojczynski appear[13] to lead to the conclusion that a pepsin solution in absence of acid is able to partially destroy malt diastase, and that when acid is present the pepsin increases the action of the latter. The diastatic activity is measured by copper suboxid reduced from Fehling solution, but the results of a series of tests are so irregular as to leave one in doubt as to their interpretation. We have carried out some tests with glycerol extracts of pancreas and with active commercial preparations from the gland. The general method of observation consisted in noting the rate and extent of action on standard starch paste of a series of pancreatic solutions, some of which were not mixed with pepsin solutions, while others received an addition of pepsin solution, in some cases boiled and in others not. In such experiments it must be kept in mind that incubation alone materially weakens the strength of amylopsin solutions. Observations must be made in sufficient number to measure and allow for this behavior. When precautions are taken to have the salt content and other conditions the same it cannot be discovered that pepsin in neutral solution has any effect on the conversion of starch by amylopsin.

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[12] Sörenson: Biochem. Ztschr., 1909, xxi and later.

[13] Wroblewski, Bednarski and Wojezynski: Beitr. z. chem. Physiol. u. Path., 1902, i, 229.

These necessary conditions are secured here by treating the diastase solution in parallel experiments by active pepsin and pepsin rendered inactive by heat. In tests made with the laboratory pancreas extracts and commercial products no definite effect could be proved.

C. THE ACTION OF PEPSIN PLUS HYDROCHLORIC ACID ON AMYLOPSIN

It has been shown above that even very weak acid has a destructive or inhibiting action on the pancreatic diastase, and that pepsin alone has little or no action on the same ferment. It remains to inquire what is the behavior of pepsin *plus* an acid of a strength below the destructive strength on the ferment. Will pepsin aided by such an extremely weak acid have any action in excess of that of pepsin alone? It is well known that as far as the action on egg albumin is concerned an acid of appreciable strength is required to bring about digestion, but a weaker acid may be sufficient to exert some effect when pepsin is present. If a weak acid retards the action of amylopsin to a certain degree, will the presence of pepsin retard it still more? This is one way to approach the question, and we have carried out a number of experiments in this direction, which are here explained.

Experiment 10.—Five portions of a glycerol extract of pancreas were made up to 100 c.c. with acid and pepsin as shown in Table 7. These mixtures were incubated through three hours at 40 C. and then 1 c.c. of each was incubated again with 25 c.c. of 1 per cent. starch paste. The results are shown in Table 7.

TABLE 7.—Digestion of Starch with Pancreas Extract, Previously Incubated with Hydrochloric Acid and Pepsin. (Experiment 10)

Test No.	HCl Mg.	Pep. Mg.	1 Per Cent. Sarch, c.c.	Conversion
1	5	100	25	No conversion
2	5	50	25	42 minutes
3	5	25	25	27 minutes
4	5	—	25	20 minutes
5	—	—	25	11 minutes

The 5 mg. of acid in 100 c.c. equal 0.005 per cent., which amount of acid was found before to have little destructive effect on the amylopsin. It may delay the reaction to the colorless end-point, but does not kill the amylopsin. The long incubation is more important than the acid in this case. With increasing amounts of pepsin we have a check on the rapidity of the conversion, and with 100 mg. of pepsin present the reaction becomes so slow as to escape notice.

Another set of experiments was arranged in a different way as shown.

Experiment 11.—Ten c.c. portions of a 1 : 10 glyceral extract of pancreas were mixed with hydrochloric acid and pepsin to make 25 c.c. of solution as shown in Table 8. These mixtures were incubated thirty minutes at 40 C. and then, after neutralization, incubated with 25 c.c. of 1 per cent. starch paste. The mixtures were tested by the iodin reaction at different intervals.

TABLE 8.—DIGESTION OF STARCH WITH PANCREAS EXTRACT, PREVIOUSLY INCUBATED (THIRTY MINUTES) WITH HYDROCHLORIC ACID AND PEPSIN AND NEUTRALIZED. (EXPERIMENT 11).

	HCl	Pepsin	Incubation with Starch and Result After Minutes				
Test No.	Mg.	Mg.	3	8	13	18	30
1	0.4	10	—	—	—	—	—
2	0.4	..	→+	+	+	+	+
3	0.8	10	—	—	—	—	—
4	0.8	..	—	—	→+	→+	→+
5	1.2	10	—	—	—	—	—
6	1.2	..	—	—	—	—	—

In the pepsin-containing mixtures the conversion of the starch is very much delayed, even with the weaker acid content. In absence of pepsin, with the lower acid concentrations, we have a distinct conversion of starch.

EXPERIMENT 12.—Same as 11, but with a preliminary incubation of ten minutes (Table 9).

TABLE 9.—DIGESTION OF STARCH WITH PANCREAS EXTRACT, PREVIOUSLY INCUBATED (TEN MINUTES) WITH HYDROCHLORIC ACID AND PEPSIN AND NEUTRALIZED. (EXPERIMENT 12)

	HCl	Pepsin	Incubation with Starch and Result After Minutes				
Test No.	Mg.	Mg.	3	8	13	18	30
1	0.4	10	—	—	—	—	—
2	0.4	..	+	+	+	+	+
3	0.8	10	—	—	—	—	—
4	0.8	..	→+	→+	→+	→+	→+
5	1.2	10	—	—	—	—	—
6	1.2	..	—	—	—	→+	→+

When the mixtures with the pepsin were given more time it was found that a partial change of the starch followed, but slowly. There appears to be, therefore, some action of the pepsin and acid which the acid alone does not possess. In a later series of experiments the method was varied by adding boiled pepsin solution in the control. This introduced the same amount of protein. But the results were of the same order. With the active pepsin present in the preliminary incubation there was a delay later in the starch digestion.

EXPERIMENT 13.—An active pepsin was used, 100 mg. to the 10 c.c. A solution of an active commercial pancreatin was made containing in 200 c.c. 1,000 mg. of the ferment, 6 mg. hydrochloric acid and 200 mg. sodium chlorid. Fifty c.c. was incubated with 5 c.c. of the pepsin solution, boiled, through thirty minutes. It was then mixed with 50 c.c. of 1 per cent. starch and incubated until the iodin reaction disappeared. This required twenty-five minutes. A second 50 c.c. was mixed with 5 c.c. of active pepsin solution and incubated the same time, and then with starch. Forty minutes were now required for the disappearance of the iodin reaction.

These various tests show clearly some action of the pepsin on the amylopsin ferment. But with commercial specimens the behavior is not always so distinct, possibly because of the varying content of inorganic salts in the latter. As the limits of acidity within which amylopsin can act at all are only narrow, it may happen that the salts will neutralize the small amount of acid so that the pepsin in turn cannot be activated. This has been the case in some tests made, and here no definite effect in the direction of retardation could be affirmed. The subject, therefore, is one which is surrounded with a considerable number of difficulties. In the normal action in the body no action of the pepsin on amylopsin is likely because of the regularly occurring neutralization, but in view of the results of the experiments it is possible that some destruction of amylopsin might occur in the stomach. It is a question of reaction and excess of acid and the balance between the different phosphates as modifiers of acidity.

2. *THE ACTION OF HYDROCHLORIC ACID AND PEPSIN ON TRYPSIN*

We have here a question much like that discussed under 1. When the action of pepsin on trypsin is referred to it should be understood that pepsin in presence of hydrochloric acid is actually in mind in the great majority of cases. It has never been demonstrated that pepsin alone has any action on trypsin. The behavior of the acid alone has been frequently studied, but we have no very clear statement as to the behavior of pepsin and the acid under conditions which are important for the present inquiry.

Much of our knowledge of the digesting power of trypsin goes back to the time of Kühne, and many workers in the experimental field as well as on the commercial scale have followed his directions. Attempts to produce trypsin by the processes originally described by Kühne[14] yield at best a very weak product, with which it is difficult to make satisfactory experiments on the behavior of acids and alkalies. The effects are in all cases modified by the presence of relatively large amounts of accompanying inert proteins. Kühne spoke of his products as being able to digest bits of fibrin rapidly, but there is nowhere any evidence as to the relative weights of fibrin and ferment employed. It is likely that he must have used very much more of crude ferment than of fibrin, unless we accept the somewhat questionable hypothesis of Mays[15] that by accident, almost, Kühne secured extracts of the beef pancreas which were of a potence not since attainable by others. It was not thought necessary at the time of these earlier investigations to add anything to the pancreas powder or extract to bring about activation, and this fact has led to some question as to the real activity of the Kühne products.

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[14] Kühne: Verhandl. d. naturh. med. Ver. zu Heidelberg, 1877, p. 194; Untersuch. a. d. physiol. Inst. d. Univ., 1878, i.

[15] Mays: Ztschr. f. physiol. Chem., 1903, xxxviii, 428.

Whatever their proteolytic power, however. Kühne mentioned that these ferment substances were extremely sensitive to acids. He stated that in the presence of 0.05 per cent. of hydrochloric acid their activity is still held, but above this destruction soon follows. This statement is sometimes misquoted and made to say that in 0.05 per cent. acid the ferment is destroyed. It was shown by other workers that a much greater acidity is necessary for actual destruction. Thus, Engesser asserted[16] that the pancreas powder made by him was able to resist an acidity of 0.5 per cent. hydrochloric acid. Of the same product Ewald says[17] that in presence of 0.3 per cent. hydrochloric acid it is able to dissolve fibrin to the condition of a turbid solution. These contradictory statements have long been quoted in the literature. It is likely that the last-named writers overlooked the fact that acid of the strength used is sufficient to bring about a partial solution of the fibrin in time. In hydrochloric acid of 0.3 per cent. strength fibrin swells to a jelly-like mass, and if enough liquid is present, slowly dissolves. It is also true that the pancreas powders as made by the Engesser process contained so much protein that they would probably neutralize a considerable amount of acid by combination.

It will be recognized that the question of the action of pepsin on trypsin must depend largely on the behavior of the acid itself with trypsin, since pepsin can be used only in acid medium. From his experiments Ewald concluded that trypsin is destroyed in acid solutions containing pepsin, and that the rapidity of destruction is proportional to the amount of pepsin present. Engesser admitted that any trypsin present as such would be quickly destroyed by acid and pepsin, but he held that in the pancreas powders the trypsin is present as a "zymogen," which has a greater resisting power toward acid and pepsin.

These views have mainly a historical interest at the present time, but it is proper to note that views almost as divergent on the two main contentions, the concentration of the acid which destroys trypsin, and the effect of pepsin and acid on trypsin, are still expressed in recent literature. Part of the difficulty in the problem seems to be due to the character of the various trypsin preparations employed by different investigators. The ferment activity of the pancreas powders made in the laboratory is often very low, and the same is true of most of the market products, as already intimated. It is commonly recognized that trypsin products, in general, have but a feeble action on raw egg albumin, but it is often overlooked that the action on boiled egg albumin is also relatively slow, although easily followed with moderately strong preparations. If tested by their action on coagulated egg, many market preparations would have to be pronounced practically inert, while with casein or fibrin a fairly sharp digesting power might be shown, as will be illustrated later.. The behavior of acid toward trypsin may be best shown by the use of fibrin or casein as a test material, rather than egg.

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[16] Engesser: Ztschr. f. klin. Med., 1880, ii, 192; Maly's Jahresber., 1880, x, 297.

[17] Ewald. Ztschr. f. klin. Med.. 1879. i. 615: Maly's Jahresber., 1880. x, 297.

In our efforts to determine the action of weak hydrochloric acid on trypsin we have used a number of products: first, a laboratory pancreas powder and a laboratory glycerol extract which had stood long enough to become active; second, samples of Gruebler's trypsin, and finally the products of some American manufacturing laboratories. The best of these, by far, is the "trypsin" of Fairchild Brothers and Foster, New York, which may be recommended for scientific investigations. Specimens which have come under our observation seem to have about four times the digesting power toward fibrin possessed by the Gruebler preparation, which is often taken as a standard for comparison. The "extract of pancreas" of the same firm, F. B. and F., is also very active, and in the experiments to follow will be often referred to.

As in the inquiry on the behavior of acid and pepsin toward amylopsin, we have also here the question of the action of acid alone to consider, and also other points as follows:

A. The action of water on trypsin.

B. The action of hydrochloric acid on trypsin.

C. The action of pepsin and acid on trypsin.

In studying the action of water or acid on trypsin we have determined the digesting power of the latter under different conditions, using egg albumin, fibrin and casein for the substratum in different experiments.

The egg albumin used for our experiments was prepared in this way: A very clear, light-colored, dry hen's egg albumin is brought into this country from China, and may be obtained from dealers. It seems to be used mainly by bakers, as are other similar products. Good samples of this product, which are not hard to secure, dissolve in distilled water to an opalescent liquid, free from lumpy particles and free from odor. When this solution is poured into a large volume of boiling distilled water, slightly acidified with acetic acid, a finely divided, perfectly white precipitate is secured, as with the solutions from fresh eggs, with this advantage, however, that the nitrogen content of the washed coagulum is pretty constant. With the very clean albumins which we have been able to secure for this purpose, the nitrogen of the washed coagulum amounts to something over 100 mg. for each gram of the original dry egg. With one lot it was practically 106 mg. This weight is more nearly constant than may be obtained by using the coagulum from ordinary storage eggs, and serves well for digestion comparisons. We have found, however, that the results obtained from some other brands of dry egg albumin were not as satisfactory. Much of the American or German "egg" albumin cannot be used at all, as it is not freely soluble.

When fibrin is used, it is prepared by thorough washing in water and disintegration in a meat-chopper set to cut very fine. The chopped mass is soaked in glycerol until the larger part of the water is removed. which is hastened by pressing out thoroughly and treating with fresh glycerol. Finally, the mass is pressed as dry as possible and preserved at a low temperature in bottles containing a small amount of toluene. The product may be kept some weeks at a low temperature, and as it is comparatively dry and uniform it may be weighed directly for a series of digestions. For one of the last lots prepared in this way, and used for experiments to be quoted, the nitrogen content of 5 gm. was found to be 162.9 mg., in the mean, corresponding to about 20 per cent. protein. It has been noticed, however, that if left in a warm room autolytic digestion of the fibrin takes place rather readily, making the product unfit for use.

Casein was employed in the form of a sodium caseinate. We used a very pure casein made in the laboratory and dissolved it in weak sodium hydroxid solution, as will be explained below. The behavior of water will be studied first.

A. ACTION OF WATER ON TRYPSIN AT DIFFERENT TEMPERATURES

In pure aqueous solution trypsin becomes inactive much more quickly than pepsin, and markedly so at elevated temperatures. In 50 per cent. glycerol, trypsin may be kept through months. As to the exact effect of elevated temperatures there is a great lack of uniformity in the views of those who have reported on the subject. From our experience with a considerable number of trypsin preparations we have come to the conclusion that the salts present are probably the most important factors in modifying the stability.

According to the older experiments of Heidenhain,[18] trypsin begins to lose its activity when warmed in aqueous solution to 35 C., but this is denied by Kühne and others.[19] Biernacki[20] states that it becomes inactive in slightly alkaline solution at 45 C. Much of the discrepancy is doubtless due to the fact that different observers have worked with products of very different degrees of purity, but another fact of equally great moment is this, that the various trypsin preparations described in the literature seem to have been extremely weak products, their activities having been measured by the solution of small amounts of fibrin or coagulated egg in digestions carried through many hours.

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[18] Heidenhain: Maly's Jahresber., 1875, v, 176; Arch. f. d. ges. Physiol. (Pflüger's), 1875, x, 557.

[19] Citation by Oppenheimer, Die Fermente, p. 114.

[20] Biernacki: Maly's Jahresber, 1891, xxi, 248.

In some experiments made to test this behavior in aqueous solution we have obtained the following results, after using the "extract of pancreas" and the "trypsin" of Fairchild Brothers and Foster, and the glycerol extract of our own production:

Experiment 14.—In Table 10 are given the digestion values obtained by incubating 100 mg. of the pancreatin (extract of pancreas) through thirty minutes at 40 C., 50 C. and 60 C., in 50 c.c. of pure water, after which treatment the liquids were brought to 40 C. and to each were added 100 mg. of sodium carbonate and 3 gm. of fibrin (nitrogen content 123.5 mg. in mean). The mixtures were incubated again through four hours at 40 C. Kjeldahl determinations were made on residue and filtrate.

TABLE 10.—Digestion Values Obtained with Pancreatin Previously Incubated, First with Pure Water and Second with Sodium Carbonate and Fibrin. (Experiment 14)

	Prelim. Digest.		Nitrogen, Milligrams		
Test No.	Temp. C.	Fibrin, Gm.	Soluble	Residue	Total
1	40	3	103.3	19.3	122.6
2	50	3	77.6	46.5	124.1
3	60	3	19.1	106.0	125.1

It will be seen that the effect of the preliminary digestions at the higher temperatures is to weaken greatly the activity of the pancreatin.

In a similar experiment with a preliminary incubation of thirty minutes at 40 C., 25 mg. of pepsin were added to the neutral solution, along with the 100 mg. of pancreatin. At the end of the half hour the mixture was acidified by the addition of 100 mg. of hydrochloric acid to the 50 c.c. Three gm. of the same fibrin were added and a new incubation was made at 40 C. At the end of forty-five minutes the digestion seemed to be complete. On filtering and making Kjeldahl determinations we found:

Soluble N	117.5 mg
Residue N	4.6 mg.
Total	122.1 mg.

Corrections were always made for the nitrogen of the ferments. It is evident that under the conditions the pancreatin has not destroyed or appreciably weakened the pepsin activity, as the fibrin digestion is here due to the latter ferment.

EXPERIMENT 15.—In a digestion test similar to 14 we used the trypsin, F. B. F., instead of the pancreatin, 50 mg. of trypsin being subjected to the preliminary incubation in 50 c.c. of water. The fibrin used was not from the same lot as the other. Final digestion, three hours. (Table 11.)

TABLE 11.—DIGESTION VALUES OBTAINED WITH TRYPSIN PREVIOUSLY INCUBATED, FIRST WITH PURE WATER AND SECOND WITH SODIUM CARBONATE AND FIBRIN. (EXPERIMENT 15)

Test No.	Prelim. Temp. C.	Fibrin Gm.	Nitrogen, Milligrams Soluble	Nitrogen, Milligrams Residue	Nitrogen, Milligrams Total
1a	40	3	56.0	.....	.....
1b	40	3	57.9	47.0	104.9
2a	50	3	39.2	65.9	105.1
2b	50	3	38.9	66.1	105.0
3a	60	3	14.0	91.0	105.0
3b	60	3	14.2	91.0	105.2

It will be noted that in this experiment the time of final digestion is three hours in place of four, and that 50 mg. of trypsin were used in place of 100 of pancreatin. But it is evident that the trypsin has suffered relatively more than the other ferment at all temperatures. This seems to be true of the stronger ferments in general. As greater activity is secured, it is often at the expense of stability.

It has been said that glycerol solutions of trypsin are stable through long periods. On diluting such extracts with water we have found that they do not long preserve their activity. Even where sterilized water was used for the dilution, we found a marked decrease in action when the solutions stood over night at room temperature. The change may be in part due to the comparative absence of inorganic matters in such dilutions. At a temperature of 40 C. these pure aqueous solutions suffered greatly.

Pancreatin solutions (F. B. and F. as used above), however, when protected with toluene, were found to be fully active after standing forty-one hours at room temperature, as shown by fibrin digestion.

In another experiment the effect of longer heating was determined.

EXPERIMENT 16.—Fifty-mg. portions of trypsin were incubated at 40 C. in a volume of 50 c.c. of water through different periods, as shown below. Then to each flask 100 mg. of sodium carbonate were added and the incubation continued through three hours at the same temperature with the addition of 3 gm. of moist fibrin which had been kept in chloroform water. Kjeldahl tests were finally made to determine the amount of digestion. (Table 12.)

TABLE 12.—DIGESTION VALUES OBTAINED FROM TRYPSIN INCUBATED, FIRST WITH WATER AND SECOND WITH SODIUM CARBONATE AND FIBRIN.

(EXPERIMENT 16)

Test No.	Prelim. Digest. Minutes	Nitrogen, Milligrams Soluble	Nitrogen, Milligrams Residue	Nitrogen, Milligrams Total
1	30	48.4	49.0	97.4
2	45	50.4	....	....
3	60	53.5	42.6	96.1
4	90	42.6	....	....
5	120	47.5	50.4	97.9
6	180	42.8	54.9	97.7

It appears that at this temperature the effect of incubation is not much greater for a period of three hours than for half an hour. Some figures from a later experiment will suggest, however, that the best results are obtained by immediate digestion.

In conversation with manufacturers of pancreatins, we have learned that the effects of temperature and solution are recognized. It is often insisted that where tests are made on such preparations they should be carried out as quickly as possible after bringing the ferment into solution. In such investigations of comparative ferment value it is evident that a temperature of 40 C. is the most satisfactory and should not be exceeded.

The Effect of the Alkali

As tryptic digestions are always carried out in an alkaline medium, it is desirable to know the action of different amounts of alkali on the ferment. A few experiments only will be offered here, as we are concerned with the one alkaline substance only, sodium carbonate. It is usually stated that trypsin is not weakened or destroyed by moderate amounts of sodium carbonate, up to about 0.5 per cent. This depends, however, on the temperature, as the following tests show. While elevation of temperature weakens the trypsin greatly, almost complete destruction follows if much alkali is present. In the following experiments portions of 100 mg. of pancreatin in a volume of 50 c.c. were incubated with and without alkali through different times at temperatures of 40, 50 and 60 C. They were then brought to the same alkalinity and incubated with 3 grams of fibrin through periods, as shown, at 40 C.

Experiment 17.—Preliminary incubation with and without alkali, using pancreatin (F. B. and F.) and 3 gm. of pressed fibrin (N content 123.5 mg.)

TABLE 13.—Digestion Values Obtained with Pancreatin Previously Incubated with and Without Alkali. (Experiment 17)

Test No.	Prelim. Alkali Mg.	Prelim. Inc. One Hr. at C.	Alkali Added Mg.	Final Inc. Hours	Result
1	...	40	100	6	Digestion completed
2	100	40	...	6	Digestion completed
3	...	40 50	100	6	Two-thirds digested
4	100	40 50	...	15	Slight digestion
5	...	40 50 60	100	15	No digestion
6	100	40 50 60	...	15	No digestion

In Nos. 1 and 2 (Table 13) the time and alkali effects are but slight, as the digestion is complete in six hours. In No. 3 the action of the higher temperature is shown in the preliminary digestion and when alkali is present at the outset the ferment seems to lose all its activity, practically, as shown in No. 4.

In Nos. 5 and 6 the temperature alone seems to be sufficient to stop digestion. These experiments were repeated a number of times with essentially the same results. Even when a smaller amount of fibrin was used and the stronger trypsin it was found that the prolonged heating with alkali above the temperature of 40 C. resulted in a marked weakening, or practical destruction of the ferment.

Finally, the effect of incubation with increasing amounts of carbonate was determined. The results show that the ferment is active in presence of a relatively large weight of this alkali.

EXPERIMENT 18.—Fifty-mg. portions of trypsin were incubated during thirty minutes with increasing amounts of carbonate, as shown. In three cases enough hydrochloric acid was then added to neutralize all but 100 mg. of the carbonate, leaving all of the same alkalinity as the first test. In the proper cases sodium chlorid was added to make all alike in this respect, and after the addition of fibrin the incubation was continued through two hours at 40 C. Kjeldahl tests were made on the filtrate and residue of the digestion.

In two of the numbers 5 and 6 (Table 14), there was no preliminary incubation with the carbonate. This was added with the fibrin at the beginning of the actual digestion. In the preliminary digestion the volume was 50 c.c., and was made to 80 c.c. in the final digestion in Nos. 1, 2, 3 and 4. In 5 and 6 the volume was 50 c.c.

TABLE 14.—DIGESTION VALUES OBTAINED WITH TRYPSIN PREVIOUSLY INCUBATED WITH VARIOUS AMOUNTS OF SODIUM CARBONATE. (EXPERIMENT 18)

Test No.	Mg. Prelim. Alk.	Mg. Final Alk.	Soluble	Residue	Total
			Nitrogen, Milligrams		
1	100	100	77.1	22.7	99.8
2	200	100	79.4	22.1	101.6
3	300	100	84.6	16.0	100.6
4	500	100	85.7	16.0	101.7
5	...	100	98.0	4.5	102.5
6	...	500	98.0	4.2	102.2

The fact is brought out pretty clearly that in the preliminary incubation, the presence of the carbonate is protective of the ferment. It is also shown that where there is no preliminary incubation the final digestion is much nearer complete. Part of the apparent effect may, however, be due to the salt added, or formed in the other cases. The important fact which is shown is that the trypsin ferment exhibits the same activity in the presence of 1 per cent. of sodium carbonate that it exhibits with 0.2 per cent. In practice digestions may be carried out within these limits with like results, as long as the temperature is no higher than here.

B. THE ACTION OF ACID ON TRYPSIN

As our object was mainly a practical one, to determine the possible part played by pepsin in aiding the acid destruction of trypsin, we have confined ourselves to a study of the behavior of hydrochloric acid. To learn the effect of pepsin on trypsin it is, of course, necessary to fix first the action of the acid with which the pepsin works and for this purpose hydrochloric acid alone comes practically into consideration. Trials have been made with both egg albumin and fibrin, and we shall quote first a few of the egg-digestion experiments to show an important point regarding the behavior of this form of protein. The sodium carbonate mentioned was always taken as anhydrous. In all cases a correction was made for the nitrogen of the ferment itself.

Experiment 19.—Fifty mg. of F. B. and F. trypsin plus coagulum from 1 gm. of egg (106 mg. nitrogen) plus 50 mg. of sodium carbonate in volume of 50 c.c. Digested ten hours at 40 C. The undissolved egg was filtered off.

Soluble N = 25.5 mg.

Experiment 20.—Fifty mg. of same trypsin plus 30 mg. of hydrochloric acid made to 50 c.c. with water and incubated one hour at 40 C. Then 100 mg. of sodium carbonate was added with the coagulum from 1 gm. of egg and the digestion continued through ten hours at the same temperature.

Soluble N = 27.2 mg.

Experiment 21.—Fifty mg. of same trypsin, plus coagulum from 1 gm. of egg, plus 200 mg. of sodium carbonate made to volume of 50 c.c. and digested ten hours at 40 C.

Soluble N = 14.8 mg.

It is apparent from these tests that egg albumin is but slowly digested by trypsin. This fact has been occasionally referred to in the literature, but it is not clearly recognized. Some observers have actually recommended the use of uncoagulated egg white for such digestion tests to determine the value of trypsin, but it is absolutely unsuitable for the purpose, as will be pointed out below. The fibrin digestion is much more rapid, as a few experiments will indicate.

Experiment 22.—Fifty mg. of same trypsin, plus 100 mg. of sodium carbonate, plus 3 gm. of fibrin (97.7 mg. of nitrogen) made to 50 c.c., and digested at 40 C. The fibrin was all dissolved in thirty minutes.

Experiment 23.—Fifty mg. of Gruebler's trypsin, plus 100 mg. of sodium carbonate, plus 3 gm. of the same fibrin, made to 50 c.c. volume and digested at 40 C. Over two hours required for complete solution.

The last experiments show the marked difference between the two kinds of trypsin, which results were duplicated by many other observations, but they show also the ease of fibrin digestion as compared with that of egg. In one of the egg experiments a small amount of hydrochloric acid was employed in a preliminary digestion with the trypsin. This amount of acid did not appear to have any inhibiting effect as far as the subsequent digestion, after neutralization, was concerned, using either egg or fibrin. With such strengths of acid in preliminary digestion the solution of the egg was always but partial, as was the case when no acid was used. But the fibrin digestion could easily be brought to completion after such treatment. It was found that a still greater degree of acidity in the preliminary incubation seemed to have but a slight action on the trypsin, when tested with fibrin, and this was shown quantitatively with the F. B. and F. ferment in the following tests:

Experiment 24.—A series of solutions was made containing in 50 c.c. 50 mg. of the trypsin and increasing weights of the acid up to 100 mg. These solutions were incubated thirty minutes at 40 C. and then mixed with enough sodium carbonate to neutralize the acid and leave 100 mg. of the carbonate present in each case. Enough sodium chlorid was added to four of the mixtures to make the content the same as in the mixture with the greatest acid originally. Finally 5 gm. of fibrin, containing 162.8 mg. of nitrogen, was added to each mixture and all were incubated five hours at 40 C. The rate of digestion appeared to be nearly uniform. At the end of the period all of the solutions were filtered and Kjeldahl determinations made on filtrate and residue. The results were as shown in Table 15.

TABLE 15.—Digestion Values Obtained with Trypsin Previously Incubated with Acid, Then Mixed with Sodium Carbonate. (Experiment 24)

			Nitrogen, Milligrams		
Test No.	HCl Mg.	Trypsin Mg.	Soluble	Residue	Total
1	60	50	156.6	7.8	164.4
2	70	50	152.3	11.5	163.8
3	80	50	151.0	11.9	162.9
4	90	50	151.4	13.4	164.8
5	100	50	151.4	10.6	162.0

It will be seen that a preliminary digestion in a medium containing 0.2 per cent. of hydrochloric acid does not destroy or practically retard the activity of the trypsin. The digestion, after neutralization, is as complete in the mixtures which contained the largest amount of acid as it is in the one with the smallest amount. The weights of total nitrogen recovered are not quite uniform. This is doubtless due to the fact that absolute uniformity in the nitrogen content of the moist fibrin could not be secured.

Experiment 25.—The preceding experiment was repeated, using a new and much dryer preparation of fibrin. Three-gram samples contained, in the mean, 168.8 mg. of nitrogen. In these tests the acid added in the preliminary incubation was greater, as shown in Table 16.

TABLE 16.—Digestion Values Obtained as in Table 15, Except for Use of a Dryer Fibrin and Larger Amount of Acid. (Experiment 25)

			Nitrogen, Milligrams		
Test No.	HCl Mg.	Trypsin Mg.	Soluble	Residue	Total
1	100*	50	18.2	154.0	172.2
2	120	50	129.3	37.5	166.8
3	140	50	139.4	25.8	165.2
4	160	50	130.7	43.5	174.2

* + 25 pepsin.

In the first of these tests the preliminary incubation of thirty minutes with pepsin, in addition to the acid present, resulted in a marked lowering of the efficiency of the trypsin in the final fibrin digestion. In the other cases the acid digestion alone, with amounts of acid reaching 0.32 per cent., shows a slight impairment only of the activity of the trypsin. For our purpose it was not thought necessary to carry the acidity beyond this last value, or to increase the time of preliminary incubation beyond thirty minutes. We have kept in mind the practical bearing of these questions on problems connected with actual conditions in the human body.

It is evident from the preceding tests that trypsin, even when not protected by a great excess of protein, is able to withstand an acidity of over 0.3 per cent. of hydrochloric acid through thirty minutes at 40 C. Somewhat similar results have recently been reported by others, to be referred to, but the weights of protein used in the final tests of the residual trypsin activity have usually been so small as to leave the question really very much in doubt. It will be recognized that in these experiments we are not dealing with the matter of the digestion by means of trypsin in acid solution. It has been shown by many observers that in presence of acid the activity of trypsin is practically nil.[21] We are simply concerned with the effect of acid on trypsin in absence of much protein.

In this connection it is in order to refer to some similar experiments carried out with casein as the substratum. Casein may be made in very pure dry form and serves as an excellent standard substance. We have used it in different ways and in this series of tests by the method of Fuld,[22] according to which a weak sodium caseinate is prepared and treated with the ferment until it no longer gives a precipitate with dilute acetic acid. Ordinarily the method has been worked with very small weights of casein, usually 4 mg. We found a larger weight preferable as a substratum, as it permits the use of stronger ferment solutions. One set of experiments may be quoted as illustrating the whole series of tests.

Experiment 26.—Our casein solution was made with the minimum amount of alkali required for the formation of the acid salt.[23] As a trypsin we used in this series the "Extract of Pancreas" of Fairchild Brothers and Foster, already referred to. Six test-tubes were charged with amounts of the pancreatin, as shown below, and to each was added 5 c.c. of 0.2 per cent. hydrochloric acid. All the tubes were incubated one-half hour at 40 C., then neutralized exactly. To each tube 6 c.c. of 0.2 per cent. casein solution was added and these, in turn, were incubated one hour and then the tests for unaltered casein were made by adding to each tube three drops of the acetic acid reagent (1 part of acid, 50 parts of alcohol, 49 parts of water). Table 17 shows the relations. It is seen that even with the weakest pancreatin concentration, and after the half-hour incubation with acid, the casein is completely changed in the final digestion.

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[21] See, for example, Chittenden and Cummins: Am. Chem. Jour., 1885, vii, 49.

[22] Verhandl. d. Ver. inn. Med., 1907, Maly's Jahresber., 1907, xxxvii, 446; 1908, xxxviii, 375.

[23] Long: Some Investigations on Salts of Casein, Jour. Am. Chem. Soc., 1906, xxviii, 372.

TABLE 17.—DIGESTION VALUES OBTAINED WITH TRYPSIN TESTED AGAINST CASEIN. (EXPERIMENT 26)

Test No.	Pancreas Ext., Mg.	Casein, Mg.	Result
1	2.0	12	Complete digestion
2	1.3	12	Complete digestion
3	0.8	12	Complete digestion
4	0.5	12	Complete digestion
5	0.3	12	Complete digestion
6	0.0	12	No apparent change

The results of this method fully confirm those previously obtained by the fibrin digestion.

C. THE ACTION OF ACID AND PEPSIN ON TRYPSIN

Having discussed the action of weak hydrochloric acid on trypsin, we now come to the practical question of the behavior of pepsin and acid working together. As shown above, we are concerned with hydrochloric acid only, as acids of lower ionization do not come into the question at all. In fact, it is essentially with the hydrogen concentration from this acid that we have to deal, and our experiments have been so arranged as to secure the concentration indicated by the percentage weights used. To this end we have used with the acid only small weights of strong ferments and no protecting protein to combine with the acid. With the addition of the pepsin in the preliminary incubation the same plan will be followed.

At the outset it was intimated that the few investigations which have been carried out to shed light on this subject have not furnished very concordant or satisfactory results. Some of them have been roughly qualitative only, not quantitative. Much of the trouble has been with the weak trypsin products employed in the tests, making it necessary to incubate through relatively long periods, and thus introduce the disturbing time and temperature factor. The weak ferments, with high protein content, combine themselves with so much acid that a further disturbing factor is introduced. It is practically useless to employ the ordinary "pancreatins" of the market in such investigations, as their trypsin content is always low, and often nil.

Among the more recent investigations in this direction which may be quoted, two will serve as illustrations.

Some extended observations have been published by Wroblewski, Bednarski and Wojczynski[24] on the behavior of ferments toward each other and toward acids and alkalies. Some of their tests were carried out with raw egg white as substratum and others suffer from other errors of method or manipulation, so that many of the results are quite meaningless. In some of their experiments the weights of ferment and egg were as two to one, apparently. From one of their series of experiments the conclusion is drawn that hydrochloric acid has a destructive action on trypsin and that pepsin increases the extent of this action. The experiments were carried out in this manner: Ten c.c., usually, of a 2 per cent. trypsin solution was acidified with hydrochloric acid to concentrations of 0.056 to 1.12 per cent. in different tests, and treated with pepsin, usually 0.1078 gm. The mixtures were incubated at 37 C. through six hours, neutralized, diluted to the same volume, brought to an alkalinity of 0.1 per cent. soda and mixed with 3 c.c. of "1 to 5" egg albumin solution for final digestion. How long the digestion was continued is not clearly stated. The weight of undigested albumin after the treatment is given for a number of experiments. This was obtained by filtering off the coagulum produced by boiling the liquids after digestion with the "right amount" of 10 per cent. acetic acid, drying and weighing. But the numerical values given are so irregular as to fail utterly to justify the conclusion of the authors in this case, as well as in others handled in this long paper.

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[24] Wroblewski, Bednarski and Wojczynski: Beitr. z. chem. Phys. u. Path., 1902, 1, 288.

Another paper, more recent than the work first cited, was read at the Indianapolis meeting of the American Chemical Society in June, 1911, by Zimmerman.[25] This paper handles the question of the mutual action of certain ferments, among them pepsin and pancreatin, and the conclusion is reached that the action of pepsin on the tryptic ferment is not marked. The reasoning of the author is not always easy to follow, and what is given as to the method does not always explain the results reported. As this paper has attracted some attention it is necessary to go over certain details, as given. In some of the experiments reported it appears that pepsin and pancreatin were mixed in 50 per cent. glycerol and allowed to stand through rather long periods. When tests were finally made it was found that both ferments were active; that is, neither had destroyed the other. No details of quantitative tests are given, however, and it is impossible to say how far one or the other may have been weakened. It is also to be remembered that reactions in glycerol are in general much weaker than in water solution, because of diminished ionization, and for this reason the comparison is not practically a fair one. Many liquids besides glycerol would have the same effect. No conclusion can be drawn from such experiments as to the behavior in the stomach, the practical question in most cases.

Zimmerman finds further that in 50 per cent. glycerol solution trypsin retains its activity in presence of 0.35 per cent. hydrochloric acid. This is probably true. But attention is not drawn to the fact that relatively large weights of the pancreatin powder are mixed with the acid, in some cases 2 gm. or more being mixed with 25 c.c. of the acid. It is evident that the action of the acid must be materially modified by the relatively great weight of inert protein present with the ferment. This is true of most of the mixtures which Zimmerman describes. The weight of ferment taken is out of all proportion to the acid or alkali the effect of which is to be determined. This is especially true of the mixtures "containing 10 per cent. each pepsin and pancreatin" and containing varying amounts of acid. For 25 c.c. we have here, practically, 5 gm. of protein to hold the acid. It is not to be wondered at that under these conditions and in presence of glycerol the ferments should have but little action on each other. While the author's conclusions are doubtless correct as far as the mixtures observed are concerned, they do not appear to be practically applicable.

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[25] Zimmerman: Jour. Indust. and Engin. Chem., 1911, iii, 750.

Our own experiments bearing on the question follow. It was shown in one of the series of tests given above on the action of hydrochloric acid on trypsin, Experiment 25, that when pepsin was present with the acid in the preliminary incubation a marked weakening of the trypsin occurred, as shown by the action of the neutralized mixture on subsequently added fibrin. This experience was many times duplicated, as illustrated by this experiment.

EXPERIMENT 27.—A solution was made containing in 50 c.c. 100 mg. of hydrochloric acid, 50 mg. of F. B. F. trypsin and 25 mg. of active pepsin (fully 3,000 test). This solution was incubated thirty minutes at 40 C. At the end of the time it was treated with enough sodium carbonate to leave an excess of 100 mg. after neutralization. This neutralization left nearly 162 mg. of sodium chlorid. Then 5 gm. of moist fibrin (with nitrogen content of 162.8 mg. in the mean) was added and digested five hours at 40 C. The soluble nitrogen obtained was 85.3 mg. and the residue left contained 77.8 mg. In similar experiments without the pepsin the soluble nitrogen from the same amount of fibrin was over 150 mg.

Experiments like the preceding show a distinct action of pepsin on trypsin. The acid present is relatively high in comparison with the total protein, so that most of it must remain actually free, and not fully combined, as in some of the experiments reported by Zimmerman.

In this connection another set of experiments in which the final test was made by the Fuld casein method may be reported, with the following as the illustration:

EXPERIMENT 28.—Twenty mg. of F. B. F. pancreatin and 5 mg. of active pepsin were incubated in 5 c.c. of 0.2 per cent. hydrochloric acid through thirty minutes. Then the acid was neutralized and portions corresponding to 2, 1.3, 0.8, 0.5 and 0.3 mg. of the pancreatin were measured out and incubated one hour with 12 mg. of casein (as sodium caseinate) in a total volume of 10 c.c. When the acetic acid test was made much of the casein was found in all the incubated flasks, showing that the pepsin had weakened or destroyed the pancreatin.

These experiments were followed by a number of others carried out in the same manner, but with longer digesting periods. In four-hour periods the digestion of the casein was found to be practically complete, suggesting a weakening, or partial destruction, rather than a complete destruction of the trypsin by the pepsin.

Following these tests a considerable number of others were made in a different way. In some of these the coagulum from the solution of dried egg albumin was used and in this manner.

Experiment 29.—Fifty mg. of trypsin, 30 mg. of hydrochloric acid, 50 mg. of pepsin in boiled solution and the coagulum from 1 gm. of egg were made to 50 c.c. and incubated one hour at 40 C. The mixture was then neutralized with 100 mg. of sodium carbonate and incubated through ten hours.

Soluble N, corrected for N of ferments = 36.4 mg.

Experiment 30.—Same as last with this exception: the pepsin solution added was not boiled.

Corrected soluble N = 26.9 mg.

The acid content is here so low that little or no peptic digestion of the egg might be expected. The digestion is probably wholly due to the trypsin, which seems to be weakened to some extent by the pepsin in the second experiment.

Experiment 31.—In a series of flasks 50 mg. of trypsin, 25 mg. of pepsin (both F. B. F.) and increasing amounts of hydrochloric acid were made to a volume of 50 c.c. The flasks were incubated at a temperature of 40 C. through thirty minutes and neutralized with enough sodium carbonate to leave an alkalinity of 0.2 per cent. of the carbonate. Salt was added to four of the flasks to make the content the same as that in the one with the highest original amount of acid. To each one 5 gm. of fibrin was added (mean nitrogen content 160.1 mg.) and a further incubation of six hours was made. The amounts of soluble nitrogen were determined as in Table 18.

TABLE 18.—Digestion Values of Trypsin Previously Incubated with Pepsin and Hydrochloric Acid, Then Neutralized. (Experiment 31)

Test No.	HCl, Mg.	Soluble N., Mg.
1	25	9.25
2	30	17.57
3	35	7.77
4	40	3.33
5	50	6.79

Controls without the pepsin showed complete digestion of the fibrin.

There appears to be here a marked destruction of the trypsin. In another set a new fibrin was used with mean nitrogen content for 5 gm. = 167.4 mg. This was incubated with the pepsin and trypsin in some cases, and in others was added after the preliminary incubation, as shown below.

Experiment 32.—In a number of flasks different weights of trypsin and pepsin (as above) and acid were made up to 50 c.c. and incubated thirty minutes at 40 C. In 1 to 6 (Table 19) the fibrin, 5 gm., was added before the incubation, and in 7, 8 and 9 after the incubation and neutralization. In all cases enough sodium carbonate was added to make the final alkalinity equal 0.2 per cent. The period of incubation after adding the alkali was four and one-half hours.

TABLE 19.—DIGESTION VALUES OF TRYPSIN INCUBATED AND NEUTRALIZED BEFORE AND SOME AFTER ADDITION OF FIBRIN

No. Test	Trypsin Mg.	Pepsin Mg.	HCl Mg.	Fibrin Gm.	Nitrogen, Milligrams Soluble	Nitrogen, Milligrams Residue
1	100	25*	35	5	159.6	7.6
2	100	...	35	5	157.9	8.1
3	100	25	35	5	159.9	6.3
4	100*	25	35	5	88.4	74.8
5	...	25	35	5	105.7	60.3
6	...	...	..	5	.....	167.4
7	50	...	40	5	lost	5.2
8	50	...	50	5	157.8	10.3
9	100	25	35	5	42.9	122.6

* The ferment was added in a boiled solution.

Nos. 1 and 2 of Table 19 show the digestive action of trypsin alone, as in one case no pepsin is present and in the other killed pepsin. We have a nearly complete solution of the fibrin. No. 3 shows practically the same result, and apparently no destruction of trypsin because this is protected by the fibrin present. There is also some digestion by the pepsin in acid solution, which obscures the effect of the trypsin to some extent. This is a mixed digestion. In No. 4 we have the effect of the pepsin and acid alone, as the accompanying trypsin was boiled. No. 5 shows a somewhat similar condition, indicating that the pepsin alone can digest but a part, less than two-thirds of the fibrin. No. 6 shows the nitrogen content of the fibrin. In Nos. 7 and 8 we have this difference in condition, that the fibrin was added after the preliminary acid diggestion, with no pepsin present. The trypsin remained active enough to digest the fibrin finally. In No. 9 trypsin and pepsin are digested together without protecting fibrin. When the latter is added later the trypsin seems to be now too weak to digest much of it. This coincides with some of the earlier tests in indicating, under these conditions, a partial destruction of trypsin by pepsin.

A much more complete destruction of trypsin is shown if the digestion in presence of acid is continued beyond an hour. As long as the temperature of digestion does not go above about 40 C., the effect of incubation in water alone is not noticeable for several hours, with most trypsins, but there seems to be some difference in products from different sources in this respect, due possibly to salt content. In weak acid, up to 0.2 per cent. hydrochloric acid, the destruction of the trypsin is not rapid.

A large number of experiments have been made to show the effect of acid and pepsin when the preliminary incubation is prolonged. In these tests the coagulum from 1 gm. of dry egg, prepared as explained above, was employed to measure the action. The mean nitrogen content of a gram was 106 mg. A few of the results from such experiments are sufficient to quote, as those from the use of larger amounts of acid or from longer incubation show, of course, the same destructive action.

EXPERIMENT 33.—In a number of flasks hydrochloric acid, pepsin and trypsin, in amounts shown below, were made up to a volume of 50 c.c. and incubated through two hours at 40 C. In some of the tests the trypsin was added in boiled solution. Then sodium carbonate was added to neutralize the acid and leave

0.2 per cent., more trypsin added, boiled or unboiled, and the coagulum from 1 gm. of egg. A new incubation was carried out through four hours, when the amount of soluble nitrogen was determined. A correction was made for the nitrogen of the ferments added. This is assumed to be all soluble.

TABLE 20.—DIGESTION VALUES OF TRYPSIN AFTER PROLONGED INCUBATION WITH PEPSIN AND ACID. (EXPERIMENT 33)

No. Test	Pepsin Mg.	Trypsin Mg.	HCl Mg.	Trypsin After Incubation Mg.	Nitrogen, Soluble,	Milligrams Residue
1a	25	100	20	100*	.....	108.4
1b	25	100	20	100*	.....	106.7
1c	25	100*	20	100	95.4	16.2
1d	25	100*	20	100	90.4	18.5
2a	25	200	20	200*	.....	108.6
2b	25	200	20	200*	.....	108.9
2c	25	200*	20	200	62.0	44.1
2d	25	200*	20	200	†	†
3a	25	100	50	100*	.....	103.9
3b	25	100	50	100*	.....	109.5
3c	25	100*	50	100	71.1	28.3
3d	25	100*	50	100	68.9	30.1

* Trypsin in boiled solution.

† Lost.

The trypsin used in the experiments Nos. 2a to 2d was a much weaker product than that used in the other cases.

These experiments show that the trypsin freshly added digests the egg very well, but after contact with acid and pepsin through two hours it is inert. We have found that some samples of trypsin or pancreatin heated with the acid of the strengths here used become inert, even when no pepsin is used. But the process of manufacture leaves some of these products with a larger amount of inorganic salts present. Three well-known brands of pancreatin of American manufacture show 6.7, 7.6 and 14.8 per cent. of ash, respectively. These facts must be kept in mind when comparisons of such products are made.

It is evident from the sum of the experiments quoted that, *in vitro*, the destructive action of acid on trypsin is much accelerated by the presence of pepsin. This action is modified to some extent by excess of protein present, and it is this fact which makes a definite statement as to what happens in the body somewhat difficult. An accumulation of acid beyond that necessary to combine with protein to form acid albumin would undoubtedly interfere with the activity of trypsin present at the same time. There appears to be no recovery of trypsin after neutralization of the inhibiting acid. In the actual conditions in the stomach the acid ordinarily accumulates beyond the protein-saturating point and would then be able to work on trypsin ingested. These experiments appear to uphold the view held by many physiologists that under practical conditions pepsin is antagonistic to the tryptic ferment.

In the course of our studies of these ferments we have had occasion to examine most of the pancreatins of American manufacture. There are numerous brands on the market, but many of them come from the same source. It has been found that while some of these have a fair amylolytic action, their tryptic power is usually low. Some are, indeed, quite inert. This must follow from the careless process of manufacture often followed, which may consist in the rapid drying of the pancreas gland, the removal of most of the fat by extraction with some convenient solvent and final grinding to powder. The temperature of drying undoubtedly is high enough to destroy the sensitive ferments. The low wholesale price at which some of these powders are sold would point to a very hasty process of manufacture. The tests prescribed by the Pharmacopeia for pancreatin do not encourage a higher strength than that usually found. The standard is low enough to suit the indifferent manufacturer. In this respect there is a curious contrast between the treatment of pepsin and pancreatin which certainly calls for correction.

These criticisms hold for the edition of the Pharmacopeia now in use, and they seem to hold for the revision of the work soon to appear. The conversion of 25 parts of starch, made into paste, to the colorless end-point by 1 part of ferment, in five minutes, is a requirement too low to have much practical value. It is not a fair standard, since there are a number of commercial pancreas products known which have a far greater degree of activity. The Pharmacopeia describes pancreatin as containing the other ferments of the pancreas, as well as the amylopsin. Why is no proteolytic standard adopted? The market grades will remain weak as long as the Pharmacopeia is silent on this point. Possibly all concerned recognize the seeming futility in making a product the strength of which is almost certain to be impaired, and perhaps destroyed, in passing through the stomach.

This point should be kept clearly in mind by physicians that the pancreatins of the market are mostly weak, and further, that if they were strong there is no certainty that they would be of much more use in actual practice, as commonly administered. The question may well be asked: Except for the purpose of curdling and partly predigesting milk, why should pancreatins be used at all? As digestive agents their usefulness is certainly of a very low order, and it is likely that there would be no practical loss in dropping pancreatin entirely from the Pharmacopeia.

As illustrating the actual strength of the best known brands in this country, the following table is given. The samples tested were collected fresh from the manufacturers in January, 1913, and examined at once as to their behavior with starch and fibrin. A year later, January, 1914, they were tested again. It has been repeatedly pointed out that the presence of certain inorganic substances is essential for the development of the maximum activity of the amylopsin. In many cases the process of manufacture leaves enough of this in the finished product, usually chlorid and phosphate, but occasionally this is not the fact and more salt should be added by the analyst. The Pharmacopeia fails in this very important provision, and the failure may sometimes lead to an improper rating of a product examined.

The starch-digesting power of the pancreatins will be given first, the different products being designated by number rather than by name. The numerical values given show the number of minutes required to convert 500 parts of starch to the colorless end-point by 20 parts of the ferment; that is, the low standard of the Pharmacopeia is taken for comparison. The amount of salt added was sufficient to insure a concentration of 0.1 per cent.

TABLE 21.—Starch-Digesting Power of Pancreatin

	Tests Made in 1913		Tests Made in 1914	
Number	No Salt Added	Salt Added	No Salt Added	Salt Added
1	3	3	...	3
2	15	5	105	27
3	5	4	15	10
4	60	15	...	10
5	5	4	...	14
6	4	4	...	5
7	10	4	*	80
8	10	4	...	25
9	5	4	...	7
10	5	4	...	4
11	†	..	..	..
12	10	4	...	..
13	15	4	...	..

* Inert.

† Low in amylopsin.

It will be seen that, when perfectly fresh, all of these samples, except one, satisfy the requirement of the Pharmacopeia, as long as sufficient salt is present. In absence of added salt half of the samples are found to be weak by this very lenient test. One year later over half of the samples are found to be weak, even with the salt, and some had become practically inert. Three samples retained their former value, and these were characterized by a high original content of inorganic matters. This is evidently a factor in the keeping quality as well as in the residual activity. It may be recalled that there are pancreas products on the market which are not sold under the name of pancreatin and which have four times the starch-converting power here shown. It is therefore evident that in actual digesting value and in keeping qualities some of these products are far from satisfactory.

We find a somewhat similar situation when we come to the consideration of the proteolytic power, as measured by the action on moist fibrin. In each test, in the first examination, 25 mg. of ferment, 2 gm. of fibrin and 50 c.c. of 0.2 per cent. sodium carbonate solution were incubated at 40 C. until the digestion was practically complete, as shown by the disappearance of all but stray flakes of the fibrin. In the tests made in 1914, 100 mg. of the ferment were taken in each case because the products had become weaker.

TABLE 22.—Proteoltyic Power of Pancreatins

	1913 Tests	1914 Tests			
No.	Digestion Time	Change in One Hour	Change in Three Hours	Primary Albumose	Secondary Albumose
1	80 minutes	Very slight	Slight	Slight	Trace
2	Apparently no change	Very slight	Very slight	None	None
3	120 minutes	Very slight	Very slight	Trace	Trace
4	720 minutes	Very slight	Very slight	Trace	None
5	100 minutes	Very slight	Very slight	Trace	None
6	40 minutes	Slight	Marked	Some	None
7	100 minutes	Slight	Marked	Some	Trace
8	Very little change	Very slight	Very slight	Trace	None
9	40 minutes	Slight	Slight	Trace	Trace
10	12 minutes	Nearly all	All gone	Large	Large
11	8 minutes	All gone	All gone	Large	Large
12	70 minutes				
13	105 minutes				

The terms primary and secondary albumose are here used in the old sense, the first denoting the precipitation by half saturation with ammonium sulphate, while the notation under secondary albumose indicates the result by completely saturating the filtrate from the primary albumose with the sulphate. The results are mostly trifling in amount.

In examples 10 and 11, Table 22, we see what may be expected from a really active tryptic preparation, but in most of the other cases the amounts of fibrin digested by the year-old specimens are very low, and probably so low as to merit no consideration. Even when fresh, most of the pancreatins are slow in their tryptic action and two are inert. The manufacturers of pancreatin have not yet learned the secret of making a product with a reasonable degree of tryptic activity, if this is indeed considered worth while in view of the probable partial destruction in the stomach.

It is evident that samples of pancreatin which have stood on drug-store shelves a year or more are liable to be very low in tryptic as well as in starch-digesting power. The question naturally presents itself, What, then, is the practical value of these preparations? Certainly, pancreatin, as now made, leaves much to be desired. It has yet to earn a place in the category of remedies which are actually useful.

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A PULMONARY ATTACK SIMULATING PRIMARY LOBAR PNEUMONIA, CAUSED BY PULMONARY EMBOLISM AND INFARCTION FROM A LATENT VENOUS THROMBOSIS *

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In the course of the past two years I have encountered several cases of acute pulmonary disease supervening in apparently healthy persons, which have been admitted to the hospital with the diagnosis of acute lobar pneumonia, but in which the subsequent course of the disease has made it evident that the true condition was that of pulmonary embolism and infarction, resulting from a venous thrombosis which, at the time of the onset of the illness, was latent. These cases would almost certainly have passed for instances of atypical pneumonia with a complicating venous thrombosis, had it not been for the fact that at this time I was interested in observing the clinical manifestations of thrombophlebitis as it occurs in the course of typhoid fever, and had been much impressed by the frequency with which pulmonary embolism occurred before any local signs of thrombosis could be detected. The results of these observations are recorded in two recent publications.[1, 2]

Before proceeding to an account of the cases which form the basis of this paper, it is desirable, for the better understanding of the subject, to call attention to certain facts which lack the widespread recognition they deserve. Most of these facts have been discussed at some length in the papers just referred to.

1. In the common forms of venous thrombosis, such, for example, as is seen as a complication of typhoid fever, and such as so often

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* From the Department of Medicine of Cornell Medical College and the Medical Service of the New York Hospital.

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[1] Conner: Pulmonary Symptoms as Premonitory Signs of Venous Thrombosis, Med. Rec., New York, April 29, 1911.

[2] Conner: A Contribution to the Symptomatology of Thrombophlebitus in Typhoid, THE ARCHIVES INT. MED., 1912, x, 534.

supervenes after childbirth and after certain surgical operations, there is regularly a period of days or even weeks during which the course of the thrombosis is either altogether latent or is indicated only by slight and equivocal symptoms; and the classical signs of phlegmasia alba dolens appear only late in the process, or may indeed be lacking altogether. The truth of these assertions is attested by various French writers on the subject (Vaquez,[3] Widal and Besancon[4]), and was demonstrated in many of my own cases. Moreover, the recent histologic studies of Aschoff[5] have shown that the formation of the primary or white thrombus is the result of the gradual deposition of blood platelets on the walls of the still patent vein, layer on layer, in a manner somewhat comparable to the formation of a bar by the deposit of silt in a flowing stream. There is reason to believe that the characteristic local signs of thrombophlebitis appear only after the occlusion of the vein has become complete, and after more or less periphlebitic inflammation has been added.

2. Pulmonary embolism and infarction is a much more frequent complication of venous thrombosis than is commonly supposed. It occurs in two quite distinct forms, which differ much in their time of appearance, their clinical course, and their prognosis. There is first the massive and usually fatal embolus caused by the separation and mobilization of a large fragment of a thrombus, occupying and occluding some such large vein as the femoral or iliac. The emboli occur late in the process of thrombosis and are fortunately rare; but because of their suddenness and the gravity of their symptoms, they are the ones to which attention has been chiefly directed. The second form of pulmonary embolus is of much more frequent occurrence. It appears early in the process of thrombosis, often, indeed, days or even weeks before the local signs of thrombophlebitis are recognizable, so that frequently it is the very first manifestation of that condition. Its symptoms are usually mild and are often interpreted as those of an ordinary pleurisy or pneumonia. These small, early emboli almost certainly arise from the separation of tiny particles from the primary, mural thrombus while the blood is still flowing in the affected vein. This thrombus, as has been said, is formed by the gradual deposit of agglutinated blood platelets, and it is easy to see how such freshly deposited clumps of platelets should be separated from the thrombus and carried away in the blood-stream to be lodged finally in the lung capillaries.

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[3] Vaquez: De la phlébite, Clin. méd. de la charité, 1894.

[4] Widal and Bezancon: Maladies des Veines, Nouveau traité de méd. et de thérap., vol. xxv.

[5] Aschoff, et al.: Beiträge zur Thrombosefrage, Leipzig, 1912.

3. Venous thrombosis occurs not so very rarely in individuals who are apparently in good health, or who at least are not obviously sick. The literature contains many instances of such thrombosis in girls with simple chlorosis, in men with gout, in cases of varicose veins of the legs, and even in persons who seem to be quite well. In some of these latter cases syphilis seems to be the underlying cause of the trouble.

If now the above mentioned facts are borne in mind; namely, the period of latency in venous thrombosis; the frequency with which pulmonary infarction occurs before the appearance of the local evidence of thrombophlebitis, and finally the occasional development of venous thrombosis in persons who are apparently in good health; the evidence furnished by the four cases now to be presented, will, it is believed, be found to be convincing that the cases were actually instances of pulmonary embolism and infarction, and were not examples of primary pneumonia, as they at first appeared to be. Unfortunately the evidence of this fact is purely clinical, as the cases all recovered; but this is true also for most of the cases of early pulmonary infarction seen with the venous thrombosis which complicates typhoid fever. Nevertheless, in these latter cases the clinical evidence is overwhelming, as a reference to the articles already referred to will show. The present cases are analogous in every respect to those already reported as complicating typhoid fever.[2]

CASE REPORTS

Case 1.—Male, 27 years old, a stationary fireman; admitted to New York Hospital March 15, 1912. Hospital No. 181686.

Family history unimportant. Scarlet fever in childhood. Gonorrhea one year ago. No other illnesses. Luetic infection denied. Drinks beer in moderation. Present illness began suddenly two days ago, while in usual good health, with sharp pain in left chest, made worse by coughing or deep breathing. About the same time he began to cough and to raise bloody sputum. Does not know whether or not he has had fever. No other symptoms. No chill. The pain in the chest, cough, and bloody sputum have continued.

Admission temperature 102 F., respirations 42, pulse 120.

Physical Examination.—Man of large frame, muscular, and well nourished. Skin and mucous membranes of good color. Pupils equal and normal. Teeth good; marked pyorrhea alveolaris. Tongue coated and moist. Throat normal. Chest well formed. Expansion somewhat restricted on left side. Respirations rapid. Right lung shows normal physical signs both front and back. Left chest somewhat hyperresonant in front. Posteriorly over the greater part of the left lower lobe there is dulness, with diminished breath and voice sounds and a few fine râles.

Heart apex beat not seen or felt. Relative dulness extends 4.3 cm. to right of midline in third space and 8 cm. to left in fifth space. Heartsounds clear. Slight accentuation of second sound over aortic area. No murmurs. Pulse equal, regular. Tension normal. Slight thickening of the palpable arteries. Liver dulness extends, in nipple line, from sixth rib to 1 cm. below costal margin. Liver edge not felt. Abdomen soft; no tenderness or muscular rigidity. Kidneys and spleen not palpable. Abdominal and cremasteric reflexes normal. Genitalia normal. Knee jerks equal and normal. No Babinski reflex. Superficial lymph-nodes not enlarged.

March 16. Pain in chest severe during night, requiring morphin. More comfortable to-day. Sputum abundant and frankly bloody. Leukocytes 10,900; polymorphonuclears 81 per cent., mononuclears 19 per cent.

March 17. Slept better. Dulness over left lower lobe posteriorly, with bronchial voice, and breath sounds heard about and below lower angle of scapula. Elsewhere feeble breath sounds. A few crepitant râles.

March 18. Still coughing and raising bloody sputum. To-day there is dulness and bronchial breathing over both lower lobes posteriorly. Much pain on coughing.

March 19. Coughing much through night. On right side posteriorly dulness from fifth space to lower angle of scapula, and flatness from this point to base of lung. About the lower angle of scapula the voice and breathing are bronchial. Below this the voice is nasal and the breath sounds faint and indistinct. On the left side posteriorly the signs are very similar to those on the right, except that the area of flatness is rather greater, and that a few râles are to be heard. Leukocytes 6,500, polymorphonuclears 66 per cent., mononuclears 34 per cent. Widal test negative.

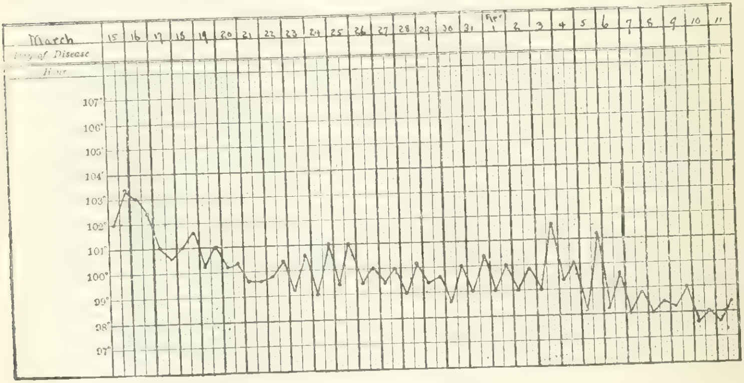

Fig. 1.—Temperature chart Case 1.

March 20. Wakeful during the night with severe sharp pain in right leg. The pain and tenderness to-day extends from the ankle up the calf almost to the knee, and there is distinct swelling of the limb. Circumference of right calf, 13 cm. below tip of patella, 34.5 cm.; of left, 32.5 cm.

March 22. Sputum still bloody. Over both chests posteriorly from one inch below angle of scapula to base there is flatness, with faint bronchial breathing, nasal voice, and greatly diminished fremitus.

March 24. Pain and tenderness in right calf have subsided. Signs in chest unchanged.

March 25. A needle inserted in lower part of right chest behind revealed no fluid.

March 26. To-day there is pain and tenderness over the anterior and inner aspects of right thigh along the course of the femoral vein.

March 29. Chest signs unchanged. Sputum still blood-tinged. Still pain and tenderness over right femoral vein. Leg edematous.

April 1. Over left chest behind there is still a small area of dulness and bronchial breathing below angle of scapula. On the right side, from seventh rib to base, the breath sounds are absent and the voice greatly diminished. Sat up in chair.

April 3. Slight dulness at base of right chest. Elsewhere the signs are almost normal. Sputum still blood-tinged.

April 9. Signs in both chests posteriorly have disappeared. Leg still edematous.

April 13. Patient discharged from hospital well, except for some edematous swelling of right leg.

The urine, on admission, was scanty and contained 1.2 gm. of albumen to the litre and many hyalin and granular casts. Later it became quite normal except for the presence of a faint trace of albumin.

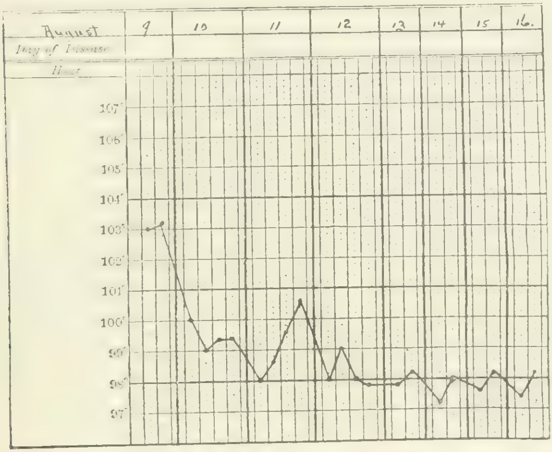

Fig. 2.—Temperature chart Case 2.

Case 2.—A man, 51 years old, an artist, was brought to the hospital by the ambulance on the afternoon of Aug. 9, 1912, with the diagnosis of lobar pneumonia. Admission temperature 103, respirations 24, pulse 96.

His father had died of cirrhosis of the liver, his mother of pulmonary tuberculosis. He himself had had two attacks of "muscular rheumatism" many years before. In 1897 he had contracted lues with secondary symptoms and had been treated for six months with mercurial inunctions and injections. In 1907 he had ulcers on his extremities and trunk which lasted almost a year. Several attacks of gonorrhea. Uses alcohol to excess, with occasional periods of abstinence.

Present Illness.—On the evening of August 7 patient had sudden cramp-like pain in the suprasternal notch along the left side of the neck to the angle of the jaw. This lasted for several hours and was somewhat relieved by hot applications. At 4 o'clock on the morning of August 9 he was awakened by very severe pain referred to the costal margin on the left side. The pain was made worse by every attempt to take a deep breath. At the same time he began to cough and to raise sputum which, at first, was streaked with blood but soon became thoroughly bloody. During the day his pain and dyspnea became so severe that an ambulance was called.

Physical Examination.—Body well developed and well nourished. Skin and mucous membranes somewhat cyanotic. Breathing labored, shallow, and painful. Pupils and ocular movements normal. Teeth fair. Tongue moist and slightly coated. Pharynx and tonsils normal. Neck shows nothing abnormal. Over both chests in front and the right chest behind, the physical signs are normal. On the left side, at the level of the lower angle of the scapula in the posterior axillary line, is a small area over which the breath sounds are bronchial. No distinct impairment of resonance or increased voice sounds. Over this area and over the entire left base, extending well into the axilla, are heard many subcrepitant râles.

The heart apex beat cannot be seen nor felt. Relative cardiac dulness extends from the right border of the sternum to 10 cm. to the left of the midline in the fifth space. Heart action regular, moderately rapid. Sounds clear and of good quality. No murmurs. Aortic second sound somewhat accentuated. Pulse of good force and normal tension. No evidence of arteriosclerosis. Liver dulness normal. Liver edge not palpable. Spleen and kidneys not palpable, and abdomen otherwise negative. Extremities: No edema. Tibiae normal. Reflexes normal. Superficial lymph-nodes not enlarged. The sputum contains a large amount of quite bright blood evenly distributed. No clots.

Leukocytes 22,500, polymorphonuclears 90 per cent., mononuclears 10 per cent. Urine normal.

August 10. Patient slept little because of the pain and cough. Somewhat more comfortable to-day. Temperature much lower. Sputum still bloody.

August 11. Sputum contains less blood. No pain in chest.

August 12. To-day no bronchial breathing to be heard over left lower lobe but the râles persist.

August 13. No blood in sputum. Pulmonary signs unchanged. Careful questioning elicits the fact that several days before the onset of the present illness he had some pain in the calf of his right leg, which soon disappeared and has not returned. In the left calf can now be felt a small indurated cord, which is not tender to pressure.

August 16. Steady improvement. Signs in left lung have disappeared. Up in chair. Several examinations of the sputum for tubercle bacilli were negative.

August 19. Discharged cured.

Case 3.—Male, 51 years old, elevator-man. Admitted to hospital January 9, 1913. No. 186327.

Family history unimportant. Since boyhood patient's general health has been good. Severe attack of tonsillitis at 24 years of age. Troublesome sciatica in right thigh from time to time for many years. Gonorrhea at 20 years. No sequelae. Denies lues. Steady drinker of beer and whisky up to two years ago. Since then has drunk very moderately.

Six weeks before admission he first felt a dull pain in the right calf, associated with slight swelling. No swelling or edema of the rest of the leg. Pain never severe enough to keep patient from work.

Present illness began on the evening of January 5 with chilliness and fever. On the following day he was seized with sudden, severe pain referred to the right upper quadrant of the abdomen and with headache and nausea. The pain soon shifted to the left upper quadrant, and has since been felt at various places in the upper part of the abdomen. In addition to the pain there has been fever, cough with scanty sputum, flatulence and abdominal distention, and quite marked dyspnea. On January 9 the patient was admitted to the surgical side of the hospital, in the service of Dr. Hitzrot.

Admission temperature 101, respirations 36, pulse 100.

At that time the marked abdominal distention, the pain referred to the epigastrium and left hypochondrium, together with some tenderness and slight muscular rigidity, suggested that the trouble was some inflammatory condition in the upper part of the abdomen. Examination of the chest revealed nothing except the presence of a few fine râles at the base of both lungs posteriorly.

The leukocytes numbered 13,800, polymorphonuclears 84 per cent., lymphocytes 13 per cent., large mononuclears 2 per cent., eosinophils 1 per cent.

January 10. Coughed a good deal through the night. Pain in lower part of left chest, especially on coughing.

For the next two days the symptoms persisted almost unchanged. The pain was located sometimes at the base of the left axilla, sometimes in the epigastrium, and sometimes in the right hypochondrium. The dyspnea continued and the cough grew more troublesome. The sputum was scanty and free from blood. On January 12 some impairment of resonance and a small area of faint bronchial breathing could be made out at the left base posteriorly, and subcrepitant râles were numerous over the lower part of both lungs. It became evident that the condition was not a surgical one, and the patient, on January 13, was transferred to the medical service, with the diagnosis of pneumonia.

Physical Examination.—Stout, well-developed man. Good color. Tongue moist and heavily coated; teeth poor; pyorrhea alveolaris. Chest broad and deep.

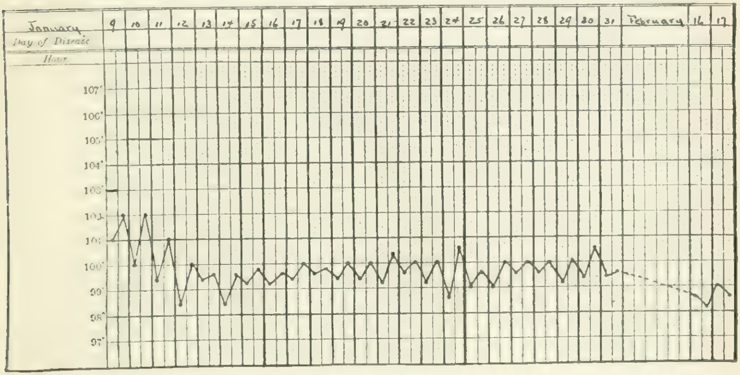

Fig. 3.—Temperature chart Case 3.

Respirations rapid, labored and painful. Lungs: Signs normal anteriorly. In left axilla is heard a coarse, leathery, friction sound. Posteriorly over the lower part of the left lower lobe the percussion note is somewhat impaired and over a small area there is distinct bronchial breathing, somewhat obscured by subcrepitant and sibilant râles, the latter heard chiefly during the much prolonged expiration. Voice sounds increased, but not frankly bronchial. Over the right base posteriorly similar râles are heard. No change in percussion, breathing, or voice sounds.

Heart much enlarged. Relative cardiac dulness extends from 5 cm. to right of midline in fourth space to about 13 cm. to left of midline in fifth space. Impulse diffuse and heaving. Heart-sounds clear. Second sound accentuated at apex and over aortic area. No murmurs. Pulse regular, somewhat rapid and strong. Systolic blood-pressure 180 mm. Arteries slightly thickened. Liver dulness extends from fourth intercostal space to costal margin. Neither liver nor spleen palpable. Abdomen full, tympanitic, and slightly tender in right upper quadrant. No muscle spasm. Genitalia normal. Extremities show no scars nor edema. Tendon reflexes normal.

January 14. The signs of consolidation at right base have disappeared. A few râles still to be heard at both bases. The urine at each examination shows a heavy precipitate of albumen (about 4 gm. to the litre), high specific gravity and many hyalin and granular casts. There is marked retention of chlorids. The phenolsulphonephthalein test shows an excretion of only 16 to 20 per cent. in two hours, and the lactose test shows the excretion of only a trace of lactose in fourteen hours.

January 21. Patient has been sitting up for two days. To-day there is pain and tenderness in right calf and over inner side of right thigh. There is also tenderness in the heel and between the first and second metatarsal bones. No edema of foot or leg. The appearance of these unmistakable signs of venous thrombosis gave the first clue to the true nature of the pulmonary lesions.

On the morning of January 26, the patient was awakened with pain in the left leg, with later tenderness in the calf and sole. During the next three days there appeared the signs of an extensive thrombophlebitis, involving the left femoral and popliteal veins, and those of the calf and foot. The signs in both legs gradually subsided in the course of the next two weeks, but some edema of both legs persisted up to the time of his discharge from the hospital, on February 22.

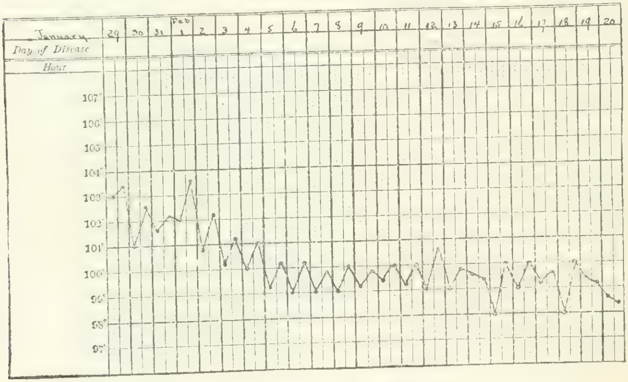

Fig. 4.—Temperature chart Case 4.

Case 4.—Female, unmarried, 63 years old. No. 186702. Admitted to the hospital on Jan. 29, 1913, with the diagnosis of lobar pneumonia.

Her present illness had begun suddenly on January 26, with severe pain in the right chest, high fever, cough, and headache. The pain was much increased by deep breathing or by coughing. The symptoms have continued, and with the cough she has occasionally spat up small amounts of clotted, bloody sputum.

Up to the time of her present illness, her general health had been remarkably good. She has had occasional attacks of cramps and diarrhea and, two months before, an attack of influenza, but otherwise had always been well.

Physical Examination.—A poorly-nourished, slender woman, with flushed face and slight cyanosis of lips. Respirations rapid and painful. The pulmonary signs over both chests in front are normal. In the right axilla a coarse friction-rub is felt and heard. Posteriorly over the lower half of the right lower lobe there is dulness on percussion, almost complete suppression of the breath sounds, and many fine crackling râles. The vocal resonance shows no distinct change.

Over the rest of the right lung and over the whole of the left lung posteriorly the signs are normal. Heart: Apex beat indistinctly felt. Relative cardiac dulness extends from the right border of the sternum to 8.5 cm. to left of the midline in the fifth space. Heart-sounds are clear. Slight accentuation of aortic second sound. Pulse small, rapid, regular, and of fairly good force. Arteries somewhat thickened. Abdomen negative. No edema of the extremities.

Admission temperature 103 F., respirations 30, pulse 108. Urine normal.

During the next two days the physical signs and the general condition of the patient remained practically unchanged. The sputum was scanty and showed small clots of dark blood. The dulness, indistinct breath sounds, and crepitant râles made it obvious that there was a localized lesion in the right lower lobe, although frank bronchial breathing was never heard.

Leukocytes 14,400, polymorphonuclears 80 per cent., lymphocytes 17 per cent., large mononuclears 3 per cent.

January 31. Condition somewhat improved and pain less. Sputum no longer bloody.

February 2. After two days and nights of comparative comfort, there is again severe pain in right side.

February 5. Signs in right lower lobe are clearing up. Still some crepitant râles to be heard. General condition much improved.

February 9. Some pain in right side during the preceding night.

February 11. Sitting up in chair.

February 16. To-day patient had sudden severe pain in left axilla where a few fine râles can be heard. The appearance of sudden pain and of râles in the other side of the chest, together with the frankly bloody character of the sputum at the onset suggested that the condition might be one of pulmonary infarction, rather than of primary pneumonia. A careful examination of the legs revealed a tender cord, about the diameter of a small lead pencil, extending along the inner side of the right thigh from a point just above the knee to the saphenous opening, and obviously representing the thrombosed internal saphenous vein. There was no periphlebitis. On being questioned the patient stated that she had noticed these "clotted veins" in the right thigh for two or three weeks, but had not spoken of them as they gave her little trouble.

On the following day the pain in the left chest was less. The râles could still be heard, but there were no signs of consolidation and but little cough.

By February 20, all the pulmonary signs had disappeared, the tenderness had gone from the thrombosed vein and the patient was able to be moved to the convalescent home at White Plains.

DISCUSSION

In Case 1 the onset was exactly like that of a primary pneumonia, except for the absence of a rigor, and no doubt was entertained at first as to the correctness of the diagnosis. But the frankly bloody character of the sputum, which continued day after day, soon raised a suspicion of the true nature of the condition, and we were able to predict with some assurance the ultimate appearance of the venous thrombosis, which gave its first local signs seven days after the onset of the pulmonary symptoms. In this instance the bloody sputum lasted for twenty-one days. Concerning the physical signs, it is to be noted that the signs of consolidation appeared first in the left lower lobe, and a few days later in the right lower lobe, and that gradually these signs changed so as to give the impression that there was present more or less fluid in both pleural cavities, although the aspirating needle failed to show any. In the above mentioned study[2] of a large number of cases of pulmonary embolism and infarction complicating typhoid fever the cases, with respect to their physical signs, could be divided into three well marked groups:

1. Those in which friction-rubs or crepitant râles, over a small area, were the only signs. These signs often lasted only two or three days.

2. Cases in which the signs were those of a small, circumscribed pneumonia. The area of consolidation did not extend, and in each instance the signs of consolidation disappeared within three or four days. These signs were almost always in the lower lobes.

3. Cases with signs of extensive plastic pleurisy or of pleural effusion. This type included more than half of all the cases. In some of these the physical signs at first were those of consolidation. It seemed quite characteristic of the third group of cases that, although the signs seemed to indicate the presence of liquid, exploratory puncture usually failed to reveal it. In the case under discussion the physical signs corresponded accurately with those in the third and largest group just quoted.

In Case 2, a luetic man, the physical signs were those of a small area of consolidation near the lower angle of the left scapula, which disappeared within two or three days. In this case also the sputum was composed chiefly of blood and bore no resemblance whatever to the rusty, tenacious sputum of pneumonia. On questioning the patient, the fact was elicited that several days before the appearance of pulmonary symptoms he had had, for a day or two, some pain in the calf of his right leg. When first seen by me, toward the end of his illness, a distinct indurated cord could be made out in the left calf, which did not correspond to any of the normal structures there, and which seemed to me clearly to represent a thrombosed and thickened vein. A very interesting feature of this case was the appearance of sudden and severe pain in the left side of the neck and in the suprasternal notch, which came on some thirty-six hours before the advent of pulmonary symptoms. The peculiar location of this pain, Capps[6] has shown to be characteristic of irritation of the central portion of the diaphragmatic pleura, and in this instance the pain suggests that there had been a small infarct somewhere on the central portion of the lower surface of the lung before the occurrence of the larger infarct, which gave the more characteristic symptoms and signs.

Case 3 was that of a man with fairly marked chronic nephritis. which, however, did not prevent him from carrying on his daily work

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[6] Capps: An Experimental Study of the Pain Sense in the Pleural Membranes. THE ARCHIVES INT. MED., 1911, viii, 717.

—an occupation that required him to be constantly on his feet. In this instance the diaphragmatic location of the infarct is seen by the fact that the symptoms (pain, tenderness and muscular rigidity) were at first abdominal rather than thoracic. In this case (the only one among the four) the sputum was very scanty and was at no time bloody. The signs of consolidation lasted only about two days. The clue to the true diagnosis came only when signs of phlebitis appeared some days after the pulmonary signs. Then was elicited the fact that, for several weeks before his illness, he had had dull pain and soreness in the right calf, with some local swelling.

In Case 4, the interesting features were the character of the sputum, and the fact that two weeks after the subsidence of the first pulmonary attack there were indications of the occurrence of a small embolus in the other lung.

To recapitulate, then, we have in three of the four cases sputum which consisted chiefly of liquid or clotted blood, and in no case sputum which bore any resemblance to the characteristic sputum of pneumonia; in every case the physical signs differed in some respect from those usual in pneumonia—in two cases by the short duration of the signs of consolidation, in one by the absence of frank signs of consolidation, and in one by the anomalous and protracted pleural signs; in all the cases there were indications that the pulmonary lesions were multiple; in none of the cases was there an introductory rigor; in three of the four cases the temperature chart bore little resemblance to the usual chart of pneumonia, and, finally, in three of the four cases there were points in the history to indicate that venous thrombosis existed before the onset of the pulmonary symptoms.

No one of these facts alone would be entitled to much weight in the attempt to differentiate these cases from those of primary pneumonia, but taken together they form a mass of evidence sufficient, I think, to warrant the conclusion that all of these cases were instances of pulmonary embolism and infarction.

How frequent such instances of pulmonary infarction in apparently healthy persons may be it is impossible to say, but the fact that four such cases were observed in a single medical service during the period of one year suggests that they are far from rare, and that they are worthy of consideration and study.[7] That it may be quite impossible at times to say positively whether the venous thrombosis, which declares itself after the appearance of the pulmonary trouble, is the cause or merely the result of this is freely admitted, but in most cases a careful study of the symptoms and a patient inquiry into the history of the case will, I believe, provide one with sufficient data to clear up the uncertainty. It is interesting to note that, forty years ago, Gerhardt,[8] in his classical study of pulmonary infarction, emphasized the fact, that "often the appearance of the embolic lung infarct furnishes the first firm support for the diagnosis of venous thrombosis."

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[7] Since this was written two additional cases of the same sort have been treated in the wards of the New York Hospital.

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[8] Gerhardt: Der hämorrhagische Infarct, Volkmann's Saml. klin. Vortr., 1875, No. 91.

THE COMPARATIVE VALUE OF CARDIAC REMEDIES[*]

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I. Introduction.
II. Effects of Digitalis on the Normal Circulation.
III. Drugs in Cardiac Insufficincy with Auricular Fibrillation.
  - *A*. Acute, in mitral disease.
  - *B*. Chronic, in mitral disease.
    - (*a*) Strophanthin.
    - (*b*) Digitalis.
  - *C*. In other rapid, fibrillating hearts.
    - (*a*) In aortic disease.
    - (*b*) In chronic nephritis.
    - (*c*) In myocardial disease.
    - (*d*) In paroxysmal tachycardia.
    - (*e*) In cases with paroxysmal dyspnea.
    - (*f*) In cases with active endocarditis.

IV. Drugs in Cardiac Insufficiency with Normal Rhythm.
  - *A*. In hypertensive cases.
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  - *E*. In failure of the right ventricle.
  - *F*. In exophthalmic goiter.

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  - *A*. In paroxysmal tachycardia.
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VI. Drugs in Angina Pectoris.
VII. The Treatment of Recent Endocarditis and Initial Cardiac Insufficiency.
VIII. Conclusions.
Bibliography.

I. INTRODUCTION

At an international congress of medicine held in the city where William Harvey announced his discovery of the circulation of the blood, in the land where Withering first made the therapeutic virtues of the foxglove the subject of scientific inquiry, it is fitting that a section presided over by the eminent therapeutist to whom we owe the nitrites should discuss the comparative value of cardiac remedies. Twelve years ago, in a similar discussion before the nineteenth congress of internal medicine at Berlin, Professor Sahli said: *"Allein die Handhabung der Digitalis ist eine grosse Kunst, und wie in jeder Kunst, so erreicht man auch hier kaum den Gipfel der Vollendung."* No more complete demonstration of this could be afforded than the added knowledge of this very drug which the clinical studies of the twelve intervening years have contributed. The literature of the clinical investigations of cardiac remedies is now so vast that an attempt to give proper credit to the workers in the field is out of the question. I shall therefore ask pardon in advance for my omissions in this respect.

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[*] Report presented before the Section on Therapeutics (Pharmacology), Physio-Therapy and Balneology of the XVII International Congress of Medicine, London, August, 1913.

The limitation of the field of inquiry is difficult. Even the digitalis bodies, the cardiac remedies *par excellence,* have important vascular and nervous actions as well. As far back as 1866, Lauder Brunton pointed out their effect on the arterioles; the subject was subsequently studied exhaustively by Gottlieb and Magnus. This action is quite selective, so that small doses, both of digitalis derivatives and of strophanthin, may dilate the renal, while constricting the intestinal vessels, as Jonescu and Loewi, Kasztan and Fahrenkamp have shown. While Heubner denies that this occurs with therapeutic doses, and Gottlieb himself does not consider it more than highly probable, the studies of Schlayer and Hedinger on the over-irritability of the arteries in experimental nephritis — and in particular the subsequent work of Hedinger — make the strongest presumption in favor of regarding these truly cardiac drugs as at times diuretic, by local vasodilatation in the kidney. This being so, it seems wiser not to exclude from the category of cardiac remedies drugs such as caffein and camphor, whose direct cardiac action is denied by some pharmacologists — Cushny, for instance — and which act mainly on the arteries and vasomotor center. The estimation of the share of heart and vessels in a circulatory disorder is not always possible. I shall therefore consider cardiac remedies rather broadly, as circulatory remedies. I shall give my experience with the various drugs in those disturbances of the circulation in which the heart plays any part, from the standpoint of their efficiency in combating definite perversions of function. From this standpoint we may arrive at greater precision in formulating the indications for and against the several remedies which, with Edens, I believe is the chief difficulty attending their use.

Since the time of Withering, every intelligent physician has recognized the clinical picture of the insufficient heart, with chronic passive congestion of the viscera and edema, as the strictest indication for the use of digitalis or its allies. It has also been clear that the most brilliant results are obtained in the rapid, irregular heart of mitral disease. Perhaps the most important contribution to cardiac pathology and therapy for the past ten years is the proof by Lewis that the *delirium cordis* of past generations, the *pulsus irregularis perpetuis* of Hering, the nodal rhythm of Mackenzie, are the ventricular manifestations of fibrillation of the auricles. This was made possible by Einthoven, whose string galvanometer has brought the disorders of the heart's rhythm into the range of exact clinical observation; and by the pioneer work of Wenckebach, Hering and Mackenzie in this field. Lewis followed this demonstration by the proof that in man the slowing and steadying of the ventricle under digitalis is due to its action on the junctional tissues, with the production of heart block, just as in von Tabora's experimental studies. Since that time the attention of English and American clinicians and pharmacologists has been focused almost wholly on the effects produced by the digitalis bodies on the cardiac rhythm, because these effects are susceptible of exact demonstration. Other effects entering into the therapeutic action of these drugs have been neglected or ignored. This attitude does not seem so common in Europe. The extreme view was expressed by Cushny in his Harvey lecture for 1911 as follows: "But I think I am safe in stating that we have no definite evidence that digitalis exerts any action apart from the inhibition in these cases of auricular fibrillation, and that the proved fact of inhibition explains all the features observed." At that time Cushny believed digitalis block to be wholly due to vagus inhibition. Recently he has reversed himself (Cushny, Morris and Silberberg). From experiments as to the degree of release after atropin, he concludes that, in normal rhythm, digitalis slowing is usually inhibitory, in fibrillating cases due to direct action on the conducting tissues, direct depression of excitability, or indirect, through improved nutrition of the heart. In a recent discussion on the treatment of non-valvular heart disease he further admits that the effect on the ventricle itself is real, but it is not possible to speak of it with certainty.

Mackenzie expresses himself with somewhat more reserve. His studies of digitalis are a model of thoroughness, and he has been foremost in bringing precision into cardiac therapeutics. He is impressed with the difference in the reaction of individual hearts to the drug, due at least in part to the nature of the lesion; yet his emphasis is entirely on the disturbance of rhythm, and he thinks little of the gross mechanical defect. In a recent text-book article he states his belief in tone increase under digitalis, though he confesses inability to demonstrate any change in the size of the heart.

Such opinions evidence a healthy scepticism, but also the inadequacy of our present clinical methods for measuring the efficiency of the circulation as a whole. The volume output of the heart we cannot even guess at. The peripheral arterial pressures give us a rough indication of the changes in mean aortic pressure, but vasomotor compensation in man is probably so much more perfect than in the lower animals, that this can in nowise be considered a measure of the heart's work. Improved coronary circulation must be an important factor in enhancing the strength of the heart muscle, whenever the aortic circulation is favorably influenced. Up to the present, our simple clinical observation of the redistribution of the blood from the venous to the arterial side of the circulation with shrinking of the swollen liver, absorption of edema with diuresis, and relief of pulmonary stasis and its attendant dyspnea, must be the evidence for the human ventricle of those systolic and diastolic effects of digitalis which are fundamental actions on the isolated heart, as Professor Gottlieb has shown. They must be subjected to searching criticism and such analysis as is possible, and checked by exact observations of rate, rhythm, blood-pressure, water exchanges, and so forth; but they cannot be supplanted by these. For a proper use of cardiac remedies, I agree with Romberg that the emphasis should be on the dynamic condition of the heart's action. Fraenkel's contributions to our knowledge of digitalis therapy have not lost their value because they preceded the era of the polygraph, nor have Huchard's opinions; but they must be amplified and corrected. I would focus your attention. therefore, on the efficiency of the circulation and our ability to influence it.

II. EFFECTS OF DIGITALIS ON THE NORMAL CIRCULATION

It seems clear from all pharmacological studies, from such experiments with long-continued digitalis administration as Cloetta's, and from Fraenkel and Schwartz's intravenous strophanthin injections in normal men, that the effects of digitalis on the normal circulation are minimal unless the drug is pushed to the point of intoxication. This fact has often been used as an argument by those who do not believe that digitalis given therapeutically increases the efficiency of the ventricular muscle. I believe, however, that we must recognize that the normal, intact circulation is already working with optimal efficiency and that the perfectly definite systolic and diastolic effects of digitalis on the isolated ventricle are not calculated to enhance this. Whether long-continued administration of digitalis can lead to hypertrophy of the heart, as claimed by Hare and Coplin, no subsequent experiments have determined with any certainty (Cloetta, Gelbart, Wynn).

III. DRUGS IN CARDIAC INSUFFICIENCY WITH AURICULAR FIBRILLATION

A. *Acute, in Mitral Disease.*—The more completely a given circulatory disturbance is dependent on a rapid rate which can be controlled by digitalis, the more brilliant is the therapeutic effect of the drug. The best example of this, in my opinion, is not the extreme cardiac insufficiency with marked chronic passive congestion after long-standing auricular fibrillation in mitral disease, but a group of cases which I regard as important to recognize clinically. They are the cases of well-compensated mitral disease, in which auricular fibrillation with great tachycardia sets in acutely. As a rule, dyspnea is inconspicuous, the symptoms being great exhaustion on exertion, dizziness, and a tendency to syncopal attacks. These are symptoms rather similar to those seen in paroxysmal tachycardia and have some resemblance to Stokes-Adams syndrome. They are presumably due, in the main, to the sudden change in the cerebral circulation. After some days, enlargement and tenderness of the liver appear, and if the condition is unrecognized and therefore untreated, as I have found it to be by the general practitioner, the full-fledged picture of the decompensated mitral heart will then become manifest later. The tachycardia in these patients can be controlled by digitalis within forty-eight hours with complete relief of the symptoms, and under long-continued digitalis medication such patients may maintain a very fair working ability for several years. It is of the highest importance that treatment be instituted before marked dilatation of the right heart and general venous stasis have ensued.

I recognize clearly that the chief factor in determining the brilliant results in these cases is the auricular fibrillation, because, as Mackenzie and Lewis have demonstrated, the His bundle is peculiarly susceptible to digitalis in fibrillating hearts, the seats of old rheumatic mitral disease. On the other hand, it seems to me equally clear that the mitral stenosis makes the rapid, irregular action especially detrimental to the efficiency of the circulation. In fibrillating types of paroxysmal tachycardia, occurring in hearts not the seat of valvular disease, the circulatory disturbance produced is usually much less marked and the therapeutic results are similarly slight. In cases of advanced mitral disease, on the other hand, while the rate may be as easily controlled, secondary changes in lungs, liver and kidneys already exist, and the extent of the valvular effect is so great as to preclude the re-establishment of even fairly efficient circulation after the rate has been brought to normal. I believe, therefore, that the three elements contributing to the result in these cases are:

1. The existence of a disorder of the rhythm, against which digitalis is absolutely effective.

2. The existence of a valve lesion, the detrimental mechanical effects of which on the circulation are peculiarly heightened by auricular fibrillation.

3. The acute character of the onset of fibrillation in a heart which would have remained well compensated for years, had not the disturbance of rhythm occurred, and which, therefore, must be considered as having had a good right ventricular myocardium.

B. *Chronic, in Mitral Disease.*—Next to these acute cases of fibrillation in response to digitalis comes the type picture of gradual cardiac insufficiency, with general venous stasis and edema. Here again, if fibrillation be present, the rapidity and completeness of the functional recovery is in almost direct proportion to the heart rate. In other words, the more these cases conform to the acute type that I have described, the more promptly does the control of the tachycardia by digitalis effect a restitution of function. On the other hand, even in rheumatic mitral disease with fibrillation, if the rate be normal or slow, the effect of digitalis treatment may not be evident until it has been administered for a week or more. In some cases, especially with marked tricuspid regurgitation and liver stasis, it may fail entirely. In other cases the drug acts only after the institution of such accessory measures as the extreme fluid and salt restriction of the Karell diet, which I have found of the utmost value. In some of these patients it is altogether probable that failure is due to defective absorption of the drug given by mouth. Ogawa has shown experimentally how markedly portal stasis interferes with the passage of digitalis from the intestine into the circulation. Meyer discusses this very fully in his recent monograph.

(*a*) *Strophanthin.*—It is in these cases of extreme secondary tricuspid regurgitation with pulsating liver that strophanthin intravenously seems the ideal method of administration. My personal experience with it has not been great. I have perhaps been backward in adopting it because of the excellent results that I can usually obtain by the Karell diet. Digitalis following this usually acts with great promptness, even where it has failed before. However, the admirable results obtained with strophanthin by Fraenkel and Schwartz, Fraenkel, Danielopolu, and Bailey, incline me to resort to it more frequently.

The indications, according to Fraenkel and Schwartz, are: (1) In all severe, threatening cardiac insufficiency, dependent on primary cardiac, not vascular or renal, disease; (2) in those cases of subacute and chronic cardiac insufficiency where the patient is so ill that one desires to relieve him in less than forty-eight hours, the time required for effects by mouth; and (3) where the condition of the stomach or bowel, preceding surgical operation, etc., makes internal administration difficult, or where idiosyncrasy to other preparations exists. I am not prepared to adopt the use of strophanthin in chronic cases, except where the existence of very urgent symptoms makes haste imperative, or where portal stasis makes failure with digitalis likely. I agree with Romberg in this respect. In the urgent cases, free venesection is a most important adjuvant measure. When such patients enter a hospital, it must always be remembered that they may have had previous, protracted ambulatory treatment with digitalis. If strophanthin in full doses is then administered, the summation of this on a small amount of digitalis already fixed in the heart may produce fatal results. Hatcher and Bailey, the most careful students of strophanthin in America, have made this point clear. That in such cases one must wait, as Romberg insists, from ten to fourteen days after the last dose by mouth was given, does not seem to me imperative if digitalis effects on the general circulation and the heart rhythm are found to be absent. It is clear, however, that a small initial dose should be given, and its effect controlled by graphic record of the rhythm. In general practice, however, great caution is wise. Deaths have occurred after strophanthin which I do not believe can be laid to its use, but Chauffard and Troisier's case was clearly a poisoning, and Agassiz's possibly so.

As to the dose, Hatcher and Bailey, and Bailey, have proved that the crystalline g-strophanthin of Thoms, or ouabain, is most certain, and has twice the strength of the amorphous strophanthin of Boehringer or Merck, which is chiefly used in Europe. The dose should not exceed 0.5 mg. in twenty-four hours, and should not be repeated without careful observation of its effects. Hatcher advocates a cat-unit standard equal to 0.1 mg. of ouabain. The intravenous dose of any strophanthin should not exceed five such cat-units.

(*b*) *Digitalis.*—The choice of a preparation of digitalis is, to my mind, largely a matter of taste, provided the one used is known to be effective. For this reason it has been and is the subject of bitter controversy, into which I shall not enter. It is clear that physiological standardization is in every way desirable, but the recent work of Schmiedeberg and of Holste casts doubt on the absolute value of the frog-unit from year to year. Standardization alone will not ensure a reliable product after the apothecary has had it on his shelves. The method of preservation is all-important, as Focke has demonstrated. Given reliable leaves, my personal preference has always been for the infusion, and Dixon's critical review of the subject confirms my opinion. Gottlieb and Ogawa found the infusion absorbed better from the bowel than the powdered leaf. My experience with it, and my father's before me, have been so favorable that I should require strong evidence to make me change. When away from a known supply of good leaves, however, I have come to advocate digipuratum as a uniform and efficient preparation, even after it has been kept for some time. The question of gastric irritation seems to me of little importance, for I rarely see vomiting, except as a later central effect. In America digalen also has been used extensively, but I have not found it reliable, some samples being inert when sold. It is ordinarily used in too small a dose, through a mistaken idea of its strength. It is too irritant for subcutaneous use. The pure digitoxin used in France, Nativelle's crystallin digitalin, I have had no experience with. At the present day the choice of a preparation, I believe, should lie between standardized leaves, given in powder, as infusion, or as tincture; or digipuratum by mouth, with the only other form of administration the intravenous injection of one of the strophanthins, preferably ouabain. Hatcher's work leaves no room for doubt that, because of its extreme variability of absorption, strophanthus should never be administered orally. One should adhere to the use of a single satisfactory preparation and know it thoroughly, rather than experiment with many, and should allow others to be guided equally by their experience.

As to dosage, I have not found the large doses used by Mackenzie and Cushny to be necessary. I prefer a moderate dose, equivalent to not over 0.1 gm. (1½ gr.) of the leaves every four hours, which will give definite slowing of the pulse and diuresis in forty-eight hours in rapid fibrillating cases. This dose I continue until the pulse falls to near 60 or becomes bigeminal; failing this, until absorption of edema is complete, or nausea, vomiting, headache or other toxic symptoms ensue. As a rule, I avoid these. A most important evidence of favorable action, which Prof. W. B. James has made of great use in the wards of the Presbyterian Hospital, is the graphic record of a simultaneously recorded heart-rate and radial pulse-rate. In rapid fibrillating hearts, the difference, which we call pulse deficit, is usually great; but with digitalis slowing, the two curves approach each other, and may finally correspond. When any of these evidences of full therapeutic action is obtained, the drug is stopped and not resumed until increasing rate or pulse deficit, or disappearance of coupled beats, show the heart to be escaping from its influence, which usually occurs in from five to ten days. Then one-half or three-quarters of the daily amount given before will control all symptoms.

In all fibrillating cases with a tendency to rapid rate, after the original digitalis course, I believe the indications for continued, so-called chronic digitalis treatment are absolute. To me they are as absolute as for continued thyroid administration in myxedema. The efficiency of such hearts depends largely on the maintenance of a normal rate. A normal rate can be obtained by perpetuating the right degree of digitalis block. Sometimes this is optimal when the coupled beats appear, but the limit of dosage has then been reached, and the wiser course in ambulant patients is to keep just below that point, with the intermission of a few days every two weeks. Each case must be considered individually, as in determining the tolerance of a diabetic for carbohydrate, and then seen from time to time. Serious breakdown may thus be prevented for years, provided the heart can be reasonably safeguarded from excessive demands or a new infection, and the lesion be not progressive.

On one point I wish to state my personal opinion unequivocally. Failure to obtain satisfactory results from digitalis therapy in the class of cases just discussed is evidence of an inefficient preparation, insufficient dosage, or an improper mode of administration. I agree entirely with Krehl that, whenever digitalis fails, a second, and then a third trial should be made with a drug obtained from another source. Furthermore, I should urge the need in some cases for employing the accessory measures to which I have alluded.

C. *In other Rapid, Fibrillating Hearts.* (*a*) *In Aortic Disease.*—While the failure of compensation in hearts the seat of old mitral endocarditis is most commonly associated with a rapid ventricular rate and fibrillation, insufficient hearts with other primary lesions occasionally fall into this category. With aortic disease it is rare, and this is probably one of the reasons why digitalis so frequently fails in aortic hearts, though not the only reason.

(*b*) *In Chronic Nephritis.*—In cardiac insufficiency secondary to hypertensive arterial disease, with or without nephritis, fibrillation is also less common. From my personal records, as I shall show subsequently, the response to treatment in these cases is less dependent on the existence or non-existence of fibrillation. I believe this is in part because such rapid rates as in mitral disease are not observed, but also because moderately rapid, irregular action is less detrimental to the delivery of a reasonable minute volume into the aorta against high pressure, than to maintaining the flow through a narrow, unyielding mitral orifice (B. Lewy). The indications for treatment in the nephritic heart, therefore, I shall consider later.

(*c*) *In Myocardial Disease.*—Some elderly people whose hearts exhibit clinically primary myocardial insufficiency show a type of fibrillating tachycardia quite similar to the mitral hearts previously described, and their response to digitalis is in my experience favorable. Schrenck has also had good results in cases of primary myocardial weakness. On the other hand, I have seen patients of this same type in whom the rapid, irregular action had existed for several years, practically without cardiac symptoms. Where a relative mitral regurgitation occurs, I am persuaded from my experience that the effect of digitalis is peculiarly favorable.

(*d*) *In Paroxysmal Tachycardia.*—So far as my personal experience goes, I have no evidence that paroxysmal tachycardia, associated with fibrillation of the auricles, reacts to drugs in any way differently from the type without fibrillation. I shall therefore consider paroxysmal tachycardia as a single therapeutic problem later.

(*e*) *In Cases with Paroxysmal Dyspnea.*—In one other type of case I have seen digitalis fail completely, in spite of the existence of rapid action and fibrillation. That is, where the picture is dominated by severe paroxysms of dyspnea and eventual lung infarcts. Autopsy on a recent, peculiarly instructive case of this kind showed extensive coronary artery disease, with infarction of the heart-wall and intracardiac thrombi as a source of pulmonary embolism. The severity of the lesion of the myocardium in such a case seems adequate explanation for the failure of any drug. The caffein derivatives were equally without effect in this patient.

(*f*) *In Cases with Active Endocarditis.*—It is likewise evident that failure to respond to digitalis on the part of a heart the seat of active inflammatory processes, as in subacute and chronic septic endocarditis, can in nowise be expected, even though fibrillation exists. In my experience, a number of the cases of mitral disease in young persons, in which treatment has been of no benefit, have belonged to this category, the disease being a progressive one.

IV. DRUGS IN CARDIAC INSUFFICIENCY WITH NORMAL RHYTHM

A. *In Hypertensive Cases.*—When we turn to hearts beating under the influence of the normal pacemaker, the effects of treatment are, as a rule, much less prompt. For this reason it is more difficult to apportion correctly the credit for benefit produced among the varying factors entering into treatment. The influence of prolonged rest, the dietetic régimen, psychic factors, must all be taken into account before concluding that any drug which has been administered has contributed largely to the result. Nevertheless, in certain cases with normal rhythm, I have seen digitalis followed by as speedy relief of symptoms as in fibrillating cases. This has been particularly true in patients with cardiac insufficiency secondary to prolonged high blood-pressure. This type of disease, considered by many as chronic nephritis, I look on, with Jores and Aschoff, from the standpoint assumed long ago by Gull and Sutton, as cases of primary sclerosis of the small arteries, the kidney being, as a rule, extensively affected, but sometimes escaping entirely.

(*a*) *Digitalis.*—When these patients develop the picture of chronic passive congestion of the viscera with edema, digitalis is as clearly indicated as it is in fibrillating mitral hearts. This is the condition called by Sahli *Hochdruckstaaung*, and my experience is in absolute accord with his, that danger from increase in the blood-pressure is purely fanciful. My cases have frequently shown a moderate fall in pressure with the onset of cardiac weakness; and I always welcome a rise of 20 or 30 mm. under digitalis as evidence of benefit, though the behavior of the pressure is quite too variable to permit of it being used as a guide. This standpoint finds corroboration in the work of Miller, Price, Burnet and Josué and Godlewski. It cannot be too strongly insisted on that dangerous increase in blood-pressure from digitalis, as used in human beings, is a superstition without any basis of clinical fact. On the contrary, a moderate hypertension, up to perhaps 180 mm. mercury, is a common accompaniment of cardiac insufficiency from any cause. With the readjustment of the circulation under digitalis, the relief of dyspnea and anxiety, and the absorption of edema, the blood-pressure usually falls in a striking manner. Redistribution of blood from the venous to the arterial side of the circulation, not increased arterial and diminished venous pressures, is what digitalis therapy produces in human beings. I believe that these cases stand second to fibrillating mitral cases in the frequency with which one may ameliorate their symptoms by the digitalis series, and this often independently of the existence or nonexistence of fibrillation. A recent report by Schrenck (from Krehl's clinic) shows equally striking success in such patients. The influence on the rate is, as a rule, not very marked, though some slowing may occur. Gallop rhythm has seemed to me rather to favor the action of the drug. Many of these patients have a relative mitral regurgitation, which complicates the mechanical circulatory defect.

In order to study more exactly the frequency of fibrillation in these cases and its relation to digitalis action, I have analyzed my records of 458 private patients with high blood-pressures, seen during the past nine years, about whom I could obtain information in June, 1912. Two hundred and thirteen of these patients have died, 57 of chronic myocardial insufficiency. At the time of my examination, 71 had evidences of cardiac incompetency, but only 8 (11.2 per cent.) had perpetual arrhythmia, of whom 4 responded well to digitalis. Six patients with normal rhythm reacted to the drug equally well, 2 of them brilliantly. Of the 246 patients still living, 25 had insufficient hearts when seen, only 2 (8 per cent.) with fibrillation. Such percentages, I feel sure, are below the frequency of fibrillation in mitral valvular disease with decomposition.

There is a possible difference in the type of disease and the reaction to treatment between the well-to-do and the laboring classes, as one may observe in other pathological conditions. An analysis of a group of my ward patients especially studied, shows 63 with insufficient hearts, of whom 24 had fibrillation at some time. Of these 24, only 7 were patients with nephritis and hypertension uncomplicated by valvular disease; of these, 5 responded to digitalis. Of 12 regular hearts with hypertension, 5 were given digitalis, and only one showed improvement. However, among 75 patients with auricular fibrillation studied electrocardiographically by Dr. Stuart Hart at the Presbyterian Hospital, only 14 had a blood-pressure above 180 mm. Hg.

In many of these patients, therefore, we cannot attribute the good effect from digitalis to its action on the rate or rhythm, but I am forced to believe that we see in them the ventricular effects, the increase in completeness of systole at the existing blood-pressure. In addition, it is quite possible that the rapid diuresis and absorption of edema occasionally seen are due to the direct vasodilator effect of the drug on the renal arterioles. It is possible also that splanchnic vasoconstriction with a redistribution of the blood, such as digitalis is able to effect in animal experiments, takes place. In any event, the phenomena bear striking witness to wide-spread action on the circulation as a whole, and cannot be interpreted, as in rapid, irregular mitral hearts, merely to the control of rate and rhythm. I have seen a patient of this type who was waterlogged and who had been having nights of suffering in spite of large doses of morphin for weeks, sleep comfortably in three days after taking 2 drams of infusion of digitalis (60 c.c.) every four hours. His dyspnea was relieved and marked diuresis occurred; the edema was completely absorbed in a week; the enlargement of the liver disappeared, and he was able to walk with comfort. He had complete relief for three months.

I should not like to be understood as maintaining that the benefit from digitalis in auricular fibrillation is obtained without any effect on the ventricle other than that depending on the reduction in rate, but only that the latter is the demonstrable and principal effect. Into the underlying, fundamental problem as to why digitalis so much more easily affects rate and rhythm in fibrillating than in non-fibrillating hearts, I cannot enter. It is at the moment the most important problem awaiting solution by the pharmacologists.

(*b*) *Caffein and Allies.*—When digitalis alone does not effect prompt improvement in such patients, the caffein diuretics come in as valuable aids. I believe that their chief effect is local, on the kidney circulation. If given intermittently in comparatively small doses, 2 gr. of caffein, 10 of diuretin or 3 of theocin, for three doses, and not repeated until one or two days have elapsed, according to the method of Romberg's clinic, they are capable of producing remarkable increase in urinary output, with absorption of edema, not only in cardiac and renal disease, but occasionally even in the ascites of cirrhosis of the liver. The work of Schlayer and the recent work of Mosenthal and Schlayer,[1] have shown how overdosage of these drugs may reverse the effect on the vessels and result in oliguria. I lay great stress on the method I have outlined as a factor in the success that may be achieved with these purin diuretics.

Besides their effect on the kidney, however, their action in combination with digitalis in certain cases suggests that their well-known property of dilating the coronary arteries may be of therapeutic importance. Braun has recently given an experimental basis for combined digitalis-caffein therapy, and I have a number of case histories which bear testimony to its value. That caffein can ever supplant digitalis in those circulatory diseases in which digitalis is indicated, I do not believe. Miller's interesting study of decompensated nephritic hearts has shown that relief of dyspnea is much more striking with digitalis; theophyllin, on the other hand, produced marked diuresis in many cases, without notably lessening the respiratory distress.

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[1] Personal communication; will be published shortly.

B. *In Primary Myocardial Insufficiency.*—This condition, without notable increase in pressure, dependent on coronary sclerosis or degenerative muscle changes, may, if it presents the clinical picture of chronic passive congestion and edema, respond to the digitalis bodies. But, again, many cases fail to respond, and it is in these patients particularly that I have seen the undesirable effects of digitalis on the heart rhythm. Such effects are heart block, which in the two cases reported by Taussig, was permanent and serious, but which may be beneficial, as in a case reported by Hewlett; fibrillation, which may then be favorably affected by digitalis; extrasystoles and bigeminal rhythm, which in these cases are usually undesirable, and the *pulsus alterans*. In a recent case of this type I have seen *pulsus alterans* regularly produced after digitalis had been given for a few days, and the patient regularly made worse by it. When these patients are refractory to the digitalis drugs, combined digitalis-caffein medication must be tried, or one of the caffein series alone, but the likelihood of benefit is not great. For their paroxysms of dyspnea, nitroglycerin or other nitrite vasodilators may give temporary relief or cut short the attack. In acute edema of the lungs, as seen in such patients, I believe nitroglycerin to be of real service; and caffein hypodermically also helps.

C. *In Mitral Disease with Regular Rhythm.*—Here, again, drugs rarely act as in the fibrillating cases. Some of these cases, as a number reported by Mackenzie, improve slowly under digitalis, without showing any effect on the heart-rate. In others, sinus arrhythmias, extrasystoles, block, and even *pulsus alterans* may be produced, accompanied by improvement in some, and not in others. The French clinicians have always held to the value of caffein in these cases, but I have not been convinced of it. Improvement is usually so slow that doubt must exist as to the value of any drug used; but digitalis up to toxic symptoms does seem to improve the dyspnea.

D. *In Aortic Disease.*—The use of cardiac drugs in aortic disease, aortic insufficiency especially, has been much fought over. Corrigan's dictum that digitalis should never be given has held sway in many minds. I cannot agree with this. In a number of instances I have seen marked and lasting benefit from digitalis in aortic insufficiency, where the clinical picture was that of chronic passive congestion and edema. The French have spoken of this as the mitral stage of aortic regurgitation, and a relative mitral regurgitation is a frequent accompaniment. Huchard held that aortic incompetency was no contra-indication to digitalis. Schrenck reports its successful use in seven out of nine cases. Romberg does not favor it in uncomplicated cases. The frequent failure, and occasional sudden death, seen during its use in aortic insufficiency, were formerly laid to slowing of the heart with attendant increase in the regurgitation during diastole. If the drug is properly used and large doses avoided, however, marked slowing does not occur.

Sahli explains the failure by assuming that aortic hearts do not produce serious symptoms, as a rule, until the mechanical defect has become very extreme. Failure is then rapid. So far as the symptoms which he means are those of general venous stasis, this assumption seems warranted.

Another factor, I believe, may be of predominant importance, namely, that most aortic regurgitation is not a chronic stationary valvular defect, but the result of a progressive disease, syphilitic aortitis, frequently associated with dilatation of the arch and with actual aneurysm. The symptoms in these cases are rarely those of venous congestion. The striking symptoms are paroxysmal in nature, anginoid pain, and attacks of intense dyspepsia. Sudden death, with or without treatment, is common. This is not the type of circulatory disorder in which digitalis can be expected to do good, and I believe that many of the sudden deaths attributed to digitalis are due to the disease itself. Apart from the treatment of these cases with salvarsan, the paroxysms often yield promptly to one of the nitrites. This condition and its treatment have recently been well studied by Longcope. I find that Hoffmann also shares my view that much of the failure of digitalis in such patients is dependent on the nature of the underlying disease. One should also remember the frequent involvement of the coronary arteries in this condition.

So far as the favorable action of digitalis in some cases of aortic insufficiency is concerned, it seems as though the so-called diastolic effects, the increased diastolic distensibility first described by Williams, and recently studied by Werschinin and by W. Straub, as his so-called "pure negative" effect, would be the action most to be desired, or a combination of this with increased completeness of systole. The production of this type of effect experimentally seems largely a function of the dosage. Such great precision of dosage is at present clinically impossible, but it seems not too much to hope that through the intravenous administration of strophanthin or pure digitalis glucosides, it may in the future be possible to arrive at the actual production of this or other especially desired effects. Zollinger's experiments on rabbits with artificially produced aortic regurgitation have shown a greater efficiency of the heart, with some increase in the diastolic filling, under digitalis.

E. *In Failure of the Right Ventricle.*—In the comparatively rare cases of isolated failure of the right ventricle, secondary to advanced emphysema, kyphoscoliosis, and so forth, digitalis is notoriously unsuccessful. In such cases, the dyspnea is dependent as much on the primary disease in the lung as on the cardiac weakness, and therefore cannot be relieved. In addition, as in so many cases of primary myocardial weakness, in aortic disease, and in some of the mitral hearts with normal rhythm, the eventual appearance of general venous congestion is the last stage in a slowly developing disproportion between the ventricular muscle and the demand it is called on to meet. The reserve force of the heart, particularly of the right ventricle, is not unlimited. Where sudden overstrain, or the sudden development of fibrillation upsets the balance, the removal of this additional interference with proper cardiac function may give prompt relief. Where no such deleterious factor enters, we must look on the functional exhaustion as the expression of anatomical lesions so extreme as to be analogous to the surgeon's category of "inoperable cases," and not blame our remedies for failure to help. When in emphysema, the occurrence of an attack of asthma on the other hand leads to acute insufficiency of the right ventricle, I believe from my experience that caffein often acts surprisingly well. Meyer endorses this view.

F. *In Exophthalmic Goiter.*—In the rapid heart of exophthalmic goiter I have not personally seen any definite effects from digitalis, except when the heart became markedly insufficient, with chronic passive congestion and edema. Then I have known it to act admirably. I have at times thought that the earlier cases were improved by continued small doses of digitalis or strophanthus, but with our present knowledge of the cardiac rhythm, I do not feel that the evidence I accepted can be relied on, and that improvement was not due to other therapeutic measures, mainly rest.

Overdosage.—In all these hearts with regular rhythm I believe that dosage should be more cautious than in the fibrillating hearts. The onset of abnormal rhythm is one guide to toxic effects. Another, which I have always heeded, is the sudden cessation of a previous diuresis. Withering himself made this a guide, and many experienced clinicians have found it of value (Meyer).

V. DRUGS IN OTHER DISTURBANCES OF RHYTHM

A. *In Paroxysmal Tachycardia.*—Practically the same considerations exist in paroxysmal tachycardia. Here it is perfectly clear that we do not possess any drug with which we can definitely cut short the paroxysm. I am in agreement with Vaquez that no form of digitalis treatment is indicated, except in very protracted attacks, when evidences of cardiac insufficiency appear, and that then intravenous strophanthin is probably the best form. That in the case cited by Edens, a patient with severe mitral disease as well, who received digitalis for five days without effect and on the sixth had a sudden fall of the rate to one-third, the result can be attributed to the drug taken, is to me most unlikely. The failure even of fibrillating paroxysmal tachycardia to respond to digitalis is one of the most difficult problems awaiting solution in this field. It shows plainly that fibrillation itself is not the sole condition determining the beneficial results of digitalis therapy. It is to be hoped that careful electrocardiographic studies of the effects of large doses of strophanthin intravenously in such attacks will shed light on the present insoluble difficulties.

B. *In Heart Block.*—The use of cardiac remedies in heart block is a subject about which much apprehension exists, largely because of theoretical considerations. In complete block the inhibitory effects of digitalis are not to be feared, and, as von Tabora's experiments have shown, it is even possible that the idioventricular rhythm may be increased by it. When cardiac insufficiency with venous stasis supervenes on complete block, digitalis is definitely indicated. Like Vaquez and Edens, I have seen great improvement following its use. As Edens remarks, in such cases one can scarcely escape the conclusion that one has observed clinically the definite systolic effects of digitalis. In partial block, Volhard has seen reassociation occur under digitalis; but complete block is so likely to result that it should be experimented with cautiously. I have recently observed such reassociation follow the use of theobromin.

C. *In Extrasystolic Irregularity.*—The treatment of extrasystolic irregularities is a subject of such complexity at the present time that consideration of it does not seem to me profitable. Certain types are improved by digitalis, as Edens has shown; others may be made worse. Frequent extrasystoles in insufficient hearts always seem to me an indication for caution in the use of digitalis remedies.

VI. DRUGS IN ANGINA PECTORIS

Closely allied to the symptom-complex presented by many cases of aortic regurgitation, is angina pectoris. Anginoid pain on exertion is evidence of an abnormal function response on the part of the heart, totally different from the syndrome of chronic passive congestion and edema. I believe that the use of the terms "myocardial insufficiency" or "asystole" should be restricted to hearts exhibiting the latter. The lack of a satisfactory theory to explain the mechanism of anginoid pain forces us to rely on clinical experience as a guide to its treatment. My experience, through my association for a number of years in the consulting office of my father, among a class of patients often afflicted with this condition, has given me the opportunity to observe the effect of treatment in many hundreds of such patients. There is not the slightest doubt in my mind that in anginoid pain on exertion, or excitement, which must not be identified completely with the intense, and often fatal, paroxysms of severe angina pectoris, the quickly acting nitrites are the sovereign and almost invariably effective remedies for the relief of the paroxysm. What is more, one may even observe that nitrites administered just before exertion is undertaken will frequently enable these patients to perform double the amount of work of which they would be otherwise capable, and without pain. My preference is for nitroglycerin, which patients can carry with them in fresh tablet form. The tablets must be taken on the tongue, not swallowed. The absorption of nitroglycerin from the mouth takes place as a rule in less than one minute; from the stomach it is much more variable and delayed. Many failures to obtain relief in anginoid pain with nitroglycerin are due to inert drugs, or to the drug being swallowed. Amyl nitrite I do not think is any more effective; it is objectionable because of the odor and the attention this attracts to the patient. All other nitrites act too slowly. In the angina of hypertensive cases, nitroglycerin is peculiarly effective, but it frequently acts well in apparent coronary angina associated with low pressure, and also in the anginal attacks of syphilitic aortitis. In some of these patients very large doses, up to 1/10 grain or more, may be necessary; and the dose is always a matter for individual experiment. The continued administration of the nitrites I do not believe has any great value. From the observation of the blood-pressure during such paroxysms, my feeling is strong that the nitrites do not give relief through their lowering of the aortic blood-pressure, for the relief usually precedes this. I am inclined to regard their favorable action as due to local dilatation of the coronary arteries, though of this one cannot be certain. My personal experience, which is in accord with that of Huchard and of Krehl, is that the continued administration of iodid in small doses is of more value in diminishing the frequency of the paroxysms than any other remedy.

In very severe angina pectoris the nitrites are clearly valueless, and morphin is the strict indication. Here it is possible that digitalis may support the heart, as some of Miller and Matthews' experiments on ligature of the coronary arteries seem to demonstrate. When anginal attacks are followed by dilatation of the heart and myocardial insufficiency of the ordinary type, the attacks regularly disappear. Under such circumstances I have had brilliant results with digitalis, as in any other type of insufficient heart. An interesting observation, which has been made by Musser, is that recovery from the ventricular insufficiency under digitalis is frequently followed by recurrence of anginal pain. One is strongly tempted here to believe that the alteration in tone of the wall of the ventricle has been the factor. I have not seen striking results from the use of theobromin as advocated by Askanazy.

VII. THE TREATMENT OF RECENT ENDOCARDITIS AND INITIAL CARDIAC INSUFFICIENCY

The use of digitalis in the very earliest stages of cardiac insufficiency has been urged by Hoffmann and Fraenkel (cited by Meyer), and especially by Romberg. I am inclined to believe in the cautious, persistent use of small doses after convalescence from acute rheumatic endocarditis, in conjunction with physical methods of treatment; but I do not feel certain of the part that digitalis plays in bringing about improvement. In the slight myocardial weakness of obese persons, of anemia, and of convalescence from severe acute illness, I doubt its usefulness. In the earlier stages of decompensation and valvular disease, without fibrillation, I believe the continued use of small doses is ordinarily desirable, not pushing to the point of producing disturbances of rhythm; but until we have better means for measuring the effects of digitalis on other functions than rhythm, scepticism of clinical evidence of improvement in such cases is perfectly legitimate.

A. *Circulatory Failure of Acute Infectious Disease.*—The treatment of the circulatory failure of acute infectious disease must recognize the predominant part played by the vasomotor system, rather than the heart, in the production of the clinical picture. The clinical syndrome, the usual failure of the pure cardiac remedies, and the experimental demonstrations of Romberg and Pässler show this. Our means of combating extreme vasomotor depression are limited. The ideal drug would be a substance acting like epinephrin, but whose effects were persistent. Such a substance we do not possess. I have seen the most amazing restoration from apparent imminent death follow the intravenous injection of epinephrin in large doses—in one case over 4 c.c. of the 1 to 1,000 solution in a little more than an hour. This was in a case of extensive bronchopneumonia, with extreme cyanosis. Life was prolonged for three days. Only in pneumonia, however, is the fleeting action of epinephrin likely to be of service. Caffein has seemed to me of benefit. Camphor is little used in America. Recent experience at the Rockefeller Institute would seem to indicate that large doses of strophanthin, to the point of toxic effects, may occasionally save life in pneumonia with circulatory failure attended by extreme tachycardia. These experiments have been conducted by Dr. Fraser under absolute electrocardiographic control; they will not be published until they are confirmed in a group of cases. The possibilities of danger are considerable, but it is to be hoped that the very thorough studies being carried on will yield a valuable and rational method of treatment. I am quite sure that in these cases digitalis by mouth is worthless, and have myself formerly been in the habit of employing it subcutaneously, which is always painful. I do, however, recognize cases in which the combination of subcutaneous digitalis and caffein has seemed to give clear clinical evidence of combating the circulatory collapse. In so protracted a disease as typhoid fever, I do not believe drugs have any value. As to the efficiency of strychnin, except as a respiratory stimulant, I am in doubt. To be of use, it certainly must be given in large doses.

VIII. CONCLUSIONS

Such a review of the comparative clinical value of cardiac remedies shows how very real has been the progress of pharmacology and therapeutics during recent years. The indications for digitalis therapy have become increasingly precise through the exact study of the cardiac rhythm. One task for the future is the elaboration of equally accurate clinical methods for the estimation of the more fundamental effects of these drugs on the ventricle, and for the analysis of their cardiac and vasomotor actions. That increasing fineness of observation can ever replace the skill and experience of the master clinician, I do not for a moment believe. Withering, depending only on his unaided sight and touch, laid down the main rules for digitalis therapy which we follow to-day. The treatment of disease is an art which will ever require greater practice to master its increasingly elaborate technic, and riper judgment to utilize the growing volume of exact analytical data which scientific methods of clinical observation are furnishing. Methods can never replace the master.

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INTERPRETATION OF THE AUSCULTATORY BLOOD-PRESSURE SOUNDS *

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The auscultatory method for the determination of arterial blood-pressure in man, described by Korotkoff in 1905,[1] has called forth numerous papers particularly from those making a clinical application of the method. There appears to be unanimity of opinion that the systolic pressure is established with the onset of the brachial sound during the fall of proximal constricting pressure, but the point of diastolic pressure, originally established by Korotkoff as coincident with the disappearance of all sound, has been variously interpreted.

In a recent paper by Taussig and Cook,[2] the literature is fully presented. These authors establish the diastolic pressure at the fourth phase in the production of the sound; that is, at the point at which, during the fall of constricting pressure, the sound changes from sharp to dull, a change which is generally recognized to occur in normal subjects just before the cessation of sound. Warfield, Hoover and Dehio support the same belief. Without intentional disregard therefore, of the writers who are in agreement with the original position taken by Korotkoff, it would seem that the balance of recent experimental evidence supports a less simple reading of diastolic pressure than the one set forth by Korotkoff. Our own results suggest, however, that the point of cessation of sound so closely approximates to the diastolic pressure that it serves all practical demands of clinical refinement. Indeed, not one of our sixteen records shows evidence of the continuation of the sound beyond the point of diastolic pressure.

METHOD

The object of our experiments was to record photographically the brachial sounds simultaneously with the records of systolic and diastolic pressures as given by the Erlanger apparatus.

We used the method of Einthoven and Geluk[3] for sound registration. An ordinary Bell telephone transmitter was placed in the primary circuit of an induction apparatus carrying a current of from 200 to 350 milliamperes. The mouthpiece of the telephone was replaced by a brass tube

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* From the Physiologic Laboratory of the Johns Hopkins University.

1. Korotkoff, N. S.: Tr. Imp. Mil. Med. Acad., St. Petersburg, 1905, xi, 365.

2. Taussig and Cook: THE ARCHIVES OF INT. MED., 1913, xi, 542.

3. Einthoven and Geluk: Arch. f. d. ges. Physiol., 1894, 57, 617.

with an adjustable lateral opening. The brass tube was connected by about 10 cm. of rubber tubing to a similar piece of brass, which served for a stethoscope bell and was fastened with tape over the brachial artery just below the blood-pressure cuff at the bend of the elbow. The capillary electrometer was in the secondary circuit, and so placed with respect to a lantern that the movement of the magnified image of the capillary of mercury could be photographed on a moving sensitized film. The size of the lateral opening and the position of the secondary coil enable the observer so to adjust the apparatus that the capillary was stationary, except when a vascular sound was being produced beneath the stethoscope bell.

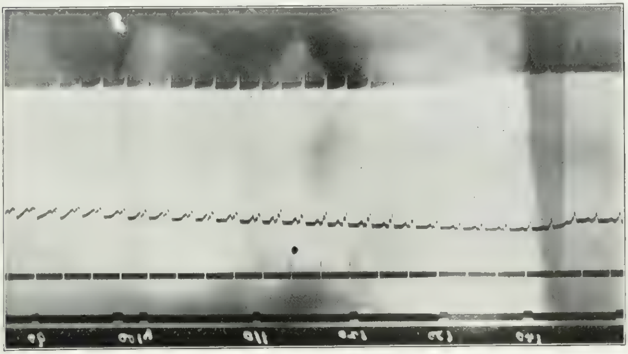

Fig. 1.—M. U. April 12, 1913. Narrow cuff. The reproduction is a mirror picture of the record. As in the following illustrations the first line shows the breaks in the shadow of the mercury capillary coincident to sounds over the brachial artery; the second line shows the pulse waves recorded by the Erlanger sphygmomanometer; the third line gives the time in seconds; the fourth line signals each 10 mm. Hg fall of pressure, the double signal marking 100 mm. Hg pressure in the constricting cuff. The record reads from right to left. It will be seen that the first sound coincides with the sudden increase of pulse magnitude (systolic pressure) and the last sound coincides with the sudden decrease of pulse magnitude (diastolic pressure).

Such adjustment is of very practical importance. It is obvious that the reliability of our results and the deductions made therefrom would be conditioned by the accuracy of the recording device employed. Such reliability would be of increased significance during the weak phases of the sound, namely, at the points of systolic and diastolic pressure. It was observed that the graphic record of sounds produced varied with the width of pressure cuff employed, but these variations corresponded with the Erlanger readings. We were finally convinced of the reliability and accuracy of our method when we attempted to apply it to the study of similar sounds produced in a circulation schema. When this device was employed the instrument recorded air vibrations which could not be detected with the ear. In other words, the instrument was at least as delicate as the ear, a fact which established beyond a doubt in our minds that we were able to record accurately the sounds produced in the brachial artery. It will be noted, too, as further evidence of the accuracy of the method that the records of sound production and pulse magnitude change at the point of systolic pressure are in absolute agreement. If the sound registration were inaccurate we should expect disagreement in the two records at this point, since observers are united that this is the point of systolic pressure.

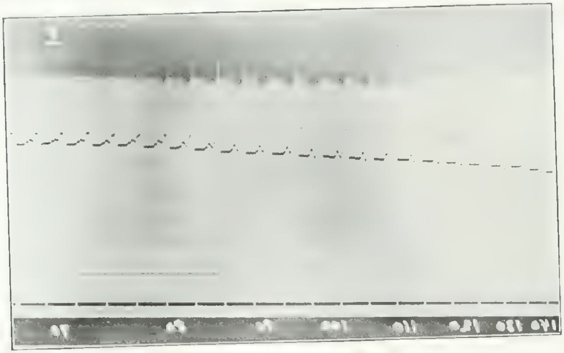

Fig. 2.—M. U. June 30, 1913. Broad cuff.

In addition to the movements of the capillary electrometer the records show (1) the shadow of the movements of the Erlanger recording lever; (2) the signal-key used to record the pressure in millimeters of mercury in the constricting cuff and (3) the time in seconds. The data thus gathered give us (1) the rate of the heart-beat; (2) the amount of constricting pressure; (3) the sudden increase in amplitude of movement of the Erlanger lever coincident with systolic pressure; (4) the sudden decrease in amplitude of movement of the Erlanger lever coincident with diastolic pressure, and (5) the relationship of the onset and disappearance of the brachial sound as shown by the shadow record of the mercury capillary to the systolic and diastolic arterial pressure as recorded with the Erlanger instrument.

The record of constricting pressure was obtained by closing a signal-key for each 10 mm. This record is thus not absolutely accurate, owing to inevitable observational error. It will be noted also in this connection that the pressure in the constricting cuff was permitted to fall with considerable rapidity. The heart-rate in all of our subjects was approximately one per second, and the rate of fall of pressure was roughly 10 mm. in three seconds. Since the criteria of systolic and diastolic pressure are found in the altered character of the sphygmomanometer record, it is obvious that the error of the method as depicted in the records here reproduced amounts to about 3 mm. of mercury. Although it would be desirable to avoid even this error, it is not a factor of great significance in blood-pressure work on man, nor in fact, in any observations in which pressure values are read in millimeters of mercury.

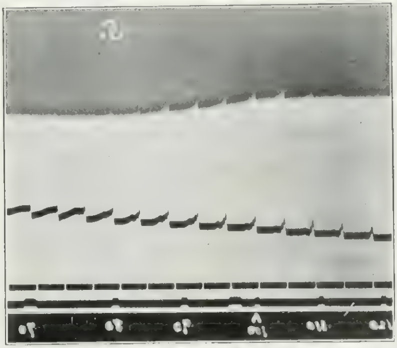

Fig. 3.—G. S. April 11, 1913. Narrow cuff.

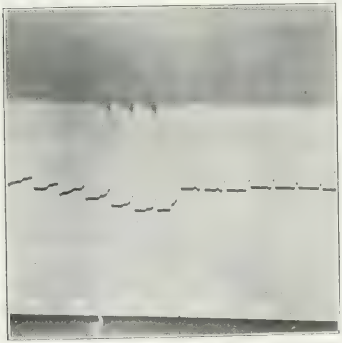

Fig. 4.—H. R. June 28, 1913. Narrow cuff.

EXPERIMENTAL

With the instrumentation above described, sixteen records were obtained from four normal individuals. The figures from the records are presented in the accompanying table. It will be seen, as is evident in the records reproduced, that there is perfect agreement between the movements of the mercury capillary and of the Erlanger lever with respect to the points of both systolic and diastolic pressures.

Table of Values for Systolic and Diastolic Arterial Blood-Pressure as Recorded by the Capillary Electrometer and the Erlanger Sphygmomanometer

Subject	Date	Cuff*	Arterial Blood-Pressure			
			By Capillary		By Erlanger	
			Systolic	Diastolic	Systolic	Diastolic
G. S.	5/11/13	†	115	75	115	75
G. S.	6/19/13	†	...	85	...	85
G. S.	6/19/13	‡	...	68	...	68
G. S.	6/25/13	‡	105	65	105	65
G. S.	6/25/13	†	135	95	135	95
M. U.	4/12/13	†	143	92	145	93
M. U.	6/30/13	‡	123	75	123	75
H. R.	6/20/13	‡	130	80	130	80
H. R.	6/20/13	†	140	95	140	95
H. R.	6/25/13	‡	120	75	120	77
H. R.	6/25/13	‡	115	85	115	85
H. R.	6/27/13	‡	115	83	115	83
H. R.	6/27/13	†	140	95	140	95
H. R.	6/28/13	‡	...	80	...	80
H. R.	6/28/13	†	130	90	130	90
C. D.	6/20/13	‡	117	85	118	85

* In this column † stands for narrow; ‡ for broad.

Two widths of cuff were used, 15 cm. and 5 cm. Although the actual pressure readings are materially higher with the narrow cuff, this factor did not disturb the agreement between the capillary and Erlanger values. It is proper to recall, however, that the broad cuff gives, as was shown by von Recklinghausen[4] and by Erlanger,[5] the more accurate figures; we made use of cuffs of different width in these observations simply to vary the experimental conditions of the test employed.

As to the causation of the brachial sound produced during observations of arterial blood-pressure we are inclined to adopt the explanation clearly set forth by Taussig and Cook, to wit, the systolic discharge of blood under the constricted area into a relatively empty section of vessel.

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4. Von Recklinghausen: Arch. f. exper. Path. u. Pharmakol., 1901, xlvi, 86.
5. Erlanger: Johns Hopkins Hospital Report, 1904, xii, 105.

We had adopted a similar view, prior to publication by these authors, based on observation of the circulation schema, already mentioned. In such a system it is not only possible to hear the sounds under consideration, but at the same time to see the behavior of the vessel wall during their production. Under different conditions the sounds produced in such a system may take on the most varied tones, intensities and time relationships which suggests that the causative factors may be as complex as those controlling the shape of the ordinary pulse-wave. We did not pursue this phase of the subject for the reason that our schema gave a pulsatile wave of pressure widely divergent in form from the normal pulse-wave in animals and man, although it would seem to promise results of interest and perhaps of practical importance in clinical medicine. If, as maintained by the authors above quoted, the brachial sound may be heard in normal subjects at a point below diastolic pressure, an adequate explanation of the phenomenon ought to be forthcoming. Our results support the original interpretation of Korotkoff.

CONCLUSIONS

1. The method of Einthoven and Geluk for the graphic registration of sounds is described and applied to the brachial sound produced in arterial blood-pressure determinations.

2. The records show a very close agreement between the results of this method and the characteristic changes observed at systolic and diastolic pressure in synchronous tracings made with the Erlanger sphygmomanometer.

3. The conclusion is therefore reached that in normal subjects the onset of the brachial sound is coincident with systolic and the cessation of the sound is coincident with diastolic arterial blood-pressure.

A PATHOLOGICAL STUDY OF TWO CASES OF HEART-BLOCK WITH ADAMS-STOKES' SYNDROME *

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In a recent very interesting report of a case of terminal heart-block, Pardee[1] demonstrates that an extensive anatomical lesion of the auriculoventricular bundle may be present without disturbance of its function. He then gives three lists: (1) ten cases, in which complete destruction of a transverse section of the bundle was invariably accompanied by complete heart-block; (2) six cases,[2] with varying degree of block, in which no lesion of the bundle existed; (3) ten cases, (six of complete and four of partial heart-block) accompanied by very slight pathological changes. The intermediate degrees of bundle involvement he has not considered. That is, though it has been firmly established that lesions of the conductive system may cause partial and complete heart-block, it seems also true that such lesions may exist (even though of considerable extent) without block; and further that partial or complete block may exist without lesion of the bundle.

The extracardiac origin of heart-block has long been suspected. Holberton[3] reported a case in which, after an injury to the neck, extreme bradycardia and "fainting fits" developed. At necropsy, adhesions pressing on the vagus were found with the heart normal. Again, Neuberger and Edinger[4] found, in a man suffering from chronic constipation, a marked bradycardia and fainting spells during defecation. The necropsy, by Weigert, disclosed a normal heart, but an infarction at the decussation of the pyramids with a small varix pressing on the nuclei and roots of the vagus. Recently it has been demonstrated[5] that stimulation of the left vagus can cause auriculoventricular dissociation.

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*From the John Herr Musser Department of Research Medicine, University of Pennsylvania.

* Submitted for publication Nov. 18, 1913.

1. Pardee, H. E. B.: The Relation of Heart-Block to Lesions of the Auriculoventricular Bundle, with Report of a Case, THE ARCHIVES INT. MED., 1913, vi, 641.

2. One of these reported by me, Adams-Stokes' Syndrome with Complete Heart-Block, without Destruction of the Bundle of His (THE ARCHIVES INT. MED., 1910, v, 583), the first reported with complete block, Pardee incorrectly states to have followed typhoid. The exact cause was never ascertained, though it followed influenza, accompanied by a long period of physical and mental strain

3. Holberton: Med.-Chir. Tr., London, 1841, Series 2, vi, 76.

4. Neuberger and Edinger: Berl. klin. Wchnschr., 1898, xxxv, 69.

5. Cohn, A. E.: Jour. Exp. Med., 1912, xv, 49.

Furthermore, it is generally conceded that ganglion cells and a rich plexus of nerve-fibers accompany the muscular system.[6] A complete pathological investigation should include, therefore, not only the sinoauricular node and the auriculoventricular system with its connections with the auricle and ventricle; but also the nerve-cells and fibers accompanying it, the vagi, and the central nervous system in neighborhood of the nuclei and roots of the vagi. This has not been done in the past for obvious reasons and will probably seldom be accomplished. It should also be remembered that even such an examination would fail to account for the functional type of block, caused by the action of toxins or deficient blood-supply.

For the purpose of determining the frequency of extensive lesions of the conductive system in the absence of heart-block, studies are now being conducted in this laboratory on appropriate post-mortem material.

In view of the increasing number of reports of heart-block, in which the clinical and pathological findings are contradictory, the following two cases are of interest, as in each case the findings at necropsy tally well with the clinical history. Unfortunately, in neither was it feasible to obtain polygraphic or electrocardiographic tracings during the period of block; but the clinical symptoms in each were of such a nature as to make it reasonably certain that at least transient block with Adams-Stokes' syndrome existed.

Case 1.—Mrs. Kate H., aged 42, a housewife, was admitted to the Philadelphia General Hospital on the service of Dr. David Riesman Jan. 1, 1913, and died January 18.

Abstract of History.—For five weeks she had had cough with scanty and at times blood-tinged sputum. The cough had gradually been getting worse. There had been no definite loss of weight. On exertion there was dyspnea; but edema was not noted. She had to rise once at night to urinate. Her menses had ceased three months before. No noteworthy symptoms referable to the gastro-intestinal system were present.

She had no recollection of any previous illness, except an attack of rheumatism in 1903, which confined her to bed for seven weeks, and a "stroke" in May, 1911, which occurred with left-side paralysis during the night. The patient had been married ten years, had had no children, no miscarriages and no venereal history. She had used alcohol (principally beer) in moderation. A brother and a sister had died of nephritis.

Examination.—The skin was yellowish and transparent, mucous membranes very pale; nutrition fair. The arteries were hard and tortuous; pulse irregular, ranging from 70 to 80 at first, although occasionally it was 25 or 40. There was a tic of the facial muscles and tongue, more marked when talking. Severe pyorrhea alveolaris and follicular deposits in the tonsils were present. At the apex of the right lung were slight dulness and harsh breath-sounds. Posteriorly both lungs were resonant, but generalized bubbling râles were heard. The cardiac apex was palpable in the sixth interspace just inside the anterior axillary line. Dulness began above at the second rib, extended on the left to the apex and on the right 1 cm. to the right of the right border of the sternum. On auscultation a loud, rough systolic murmur was heard at the pulmonary area, with reduplication and accentuation of the second sound; also a soft systolic murmur at the apex, not heard in the axilla or back. The abdomen was tympanitic. Tenderness could not be elicited and no organs or masses could be felt. The urine was reported negative, specific gravity 1.012.

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[6] Wilson: Proc. Royal Soc., 1909, lxxxi, Series B, 141.

Course.—January 8 the patient had a fainting spell. The patient next to her did not notice any convulsive movements. The pulse at 4:30 and 7 p. m. was 34. There were no visible pulsations in the neck.

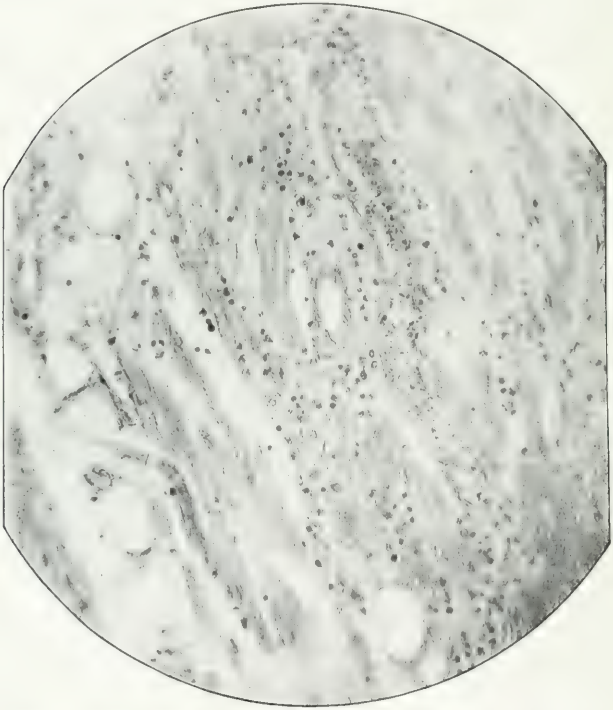

Fig. 1—Case 1, heart 31: cellular infiltration of main bundle (more marked around small blood-vessel). Zeiss DD, eye-piece 4.

January 16 the resident physician observed the patient in an epileptiform attack. The breathing was stertorous, the head was drawn to the left and the left arm twitched momentarily. The pulse dropped from 60 to 24, the patient was mentally confused and poorly oriented. The following day several attacks occurred, one of which was observed by Dr. Farr. Both arms moved slightly and the eyes turned upward. There was a brief period of unconsciousness and afterward the patient complained that everything looked black. Dr. John H. Musser, Jr., took a polygraphic tracing on this date after an attack, but found no evidence of heart-block. The pulse was then 60. The following day the patient died.

Clinical Diagnosis.—Chronic myocarditis, mitral insufficiency. Adams-Stokes' syndrome, pulmonary edema, old hemiplegia (embolic).

Anatomical Diagnosis.—In addition to the preceding, mitral stenosis, sclerotic and infarcted kidneys.

Gross and Microscopic Examination.—Heart 31, hardened in formaldehyd. Weight 390 gm. Moderate amount of fat in epicardium. Coronary vessels slightly sclerosed. Left ventricle 10 to 14 mm. thick, cuts with increased resistance and numerous fibrous threads can be seen running through the musculature. On the septal surface the endocardium is diffusely thickened and opaque, as if by extension from the thickened mitral valve, but especially over the ramifications of the left branch of His' bundle. Similarly in the right ventricle there is fibrous thickening at the bases of the chordae tendinae in the septum. The surface of the septum shows a dense mass of fibrous tissue in its middle, and near the insertion of the mitral valve a cartilaginous, almost calcified mass. The aortic valves are distinctly thickened, irregular and calcified. Small patches of sclerosis are seen on the intima of the aorta. The mitral valve is in the form of a distinct "buttonhole," the opening being about 5 by 15 mm. The pulmonary and auriculoventricular valves are normal.

HISTOLOGICAL STUDY OF HIS' BUNDLE AND KEITH'S NODE

A section 3 cm. long and 3 cm. wide was cut from the septum to include Tawara's node, His' bundle and its bifurcation. The anterior and posterior borders of the piece are almost parallel with the long axis of the right ventricle, the inferior being slightly more anterior. Considering the heart as being upright in the body, oblique (almost sagittal) serial sections were cut from behind, forward and up. About one thousand were cut, of which five hundred were mounted and about one hundred and fifty stained. Every fourth slide was stained with hematoxylin and eosin, and the succeeding slide with Mallory's anilin-blue. In all the sections both auricle and ventricle appear, with the delicate auriculoventricular valve on the right side, and the thick stumps of the aortic and mitral valves on the left.

In the earlier sections (that is, posterior) the network of Tawara's node is well shown, lying close to the fibrous base of the mitral valve. Herein are considerable delicate fibrous connective-tissue and occasionally small collections of fat-cells, but this picture shows nothing definitely abnormal. The cellular infiltrate, however (small round cells and plasma cells), is distinctly more than is ever seen in normal tissue. As far as can be ascertained, after the fixation in formaldehyd, the muscle-fibers of the node, their connection with the auricular musculature and the auricular musculature itself are normal, with characteristic narrow fibers, faint cross striations, numerous nuclei and loose connective tissue in normal amounts.

In its course through the auriculoventricular groove, the structure of the bundle cannot be well studied, but the cellular infiltrate is still noticeable.

Lower down, where the main bundle sits on the ridge of the ventricular septum (owing to the plane of the section the bifurcation appears in the same sections), the fat and cellular infiltration is well shown. The right branch can be followed for a short distance imbedded in the ventricular musculature and then disappears, enveloped on three sides by a dense mass of scar tissue (Fig. 2). The sections above and below this show that it is a real obliteration. The left lies superficially beneath the endocardium and also shows the increased number of cells.

Histological Diagnosis.—Chronic interstitial myocarditis and valvulitis (aortic and mitral), cellular and fatty infiltration and fibrosis of His' bundle.

CASE 2.—Mrs. Hattie R., aged 41, a housewife, was admitted to the Presbyterian Hospital on the service of Dr. R. Pemberton, March 3, 1913, complaining of dyspnea.

History.—The usual symptoms of a chronic, severe heart-trouble were present; namely, dyspnea, edema of the legs and abdomen and occasional palpitation and precordial pain, so severe that she could hardly walk. For three months she had had a severe cough. Four years before admission she had a febrile attack of rheumatism, sufficiently severe to confine her to bed for some days. Except for the usual diseases of childhood, her history and that of her family were negative.

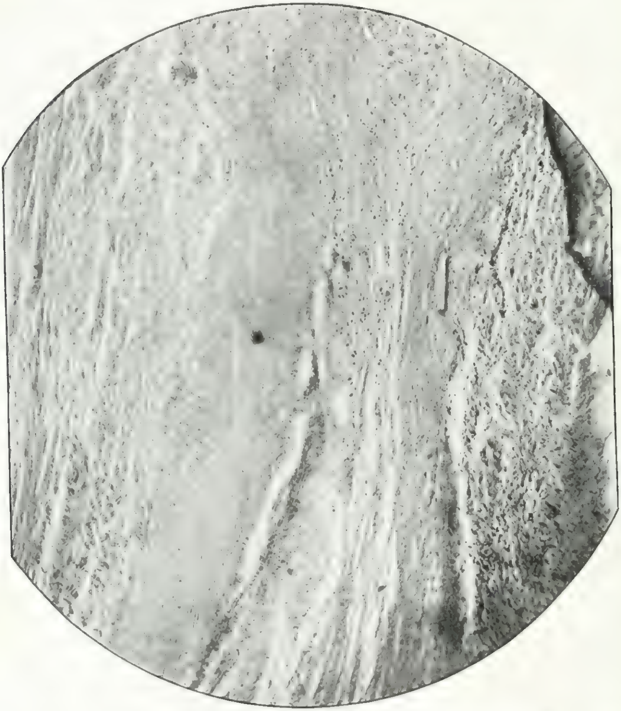

Fig. 2.—Case 1, heart 31; right branch, obliterated by fibrous tissue. Zeiss A, eye-piece 4. Two vertical bands of fibrous tissue (more dense and homogeneous than the surrounding myocardium) enclose the right branch of His' bundle. Near the center of the figure some cellular infiltrate appears in the muscle bundle, and just above this the two bands of fibrous tissue meet to obliterate it.

Examination.—On admission her temperature was 99, pulse 108, respiration 38. Cardiac dulness extended from 1 cm. beyond the right border of the sternum to 2 cm. to the left of the midclavicular line. A presystolic murmur was noted with an accentuated second pulmonic sound. There was movable dulness in the abdomen and edema of the legs. Examination of eye fundi showed hemorrhagic retinitis. The urine contained a cloud of albumin and numerous hyalin casts. The Wassermann reaction was negative.

Course.—After three weeks of aggravation, and then of amelioration of the cardiac symptoms, fever set in with a leukocytosis of 26,000, and pelvic inflammation was diagnosed. On the day of her death, four typical Adams-Stokes' attacks were observed by Dr. Pemberton. With the pulse at 48, a violent epileptiform convulsion occurred, with loss of consciousness, jerking of limbs, bulging eyes, protruding tongue and stertorous breathing, and lasted perhaps three minutes. The pulse dropped to 14, but returned to the former rate after the attack. After recovering sufficiently to ask questions, she suffered another similar attack in which the pulse dropped to 24. In the third attack it was noted that the heart stopped entirely for some seconds; in the fourth and fatal attack, respirations stopped two minutes after the cessation of the heart-beat. No opportunity was offered for graphic registration of heart-beat and pulse. Necropsy was performed by Dr. C. B. Farr four hours after death.

Anatomical Diagnosis.—Double pyosalpinx, acute seropurulent peritonitis, acute fibrinous pericarditis and pleuritis with right-sided effusion; hypertrophy and dilatation of heart; mitral stenosis; atheroma of aorta; chronic diffuse nephritis; chronic passive congestion of liver and spleen; parenchymatous degeneration of liver.

Gross and Microscopic Examination.—Heart 15, received in formaldehyd, weight 650 gm. Parietal and visceral pericardium much thickened with heavy deposits of fibrin, obscuring the various relations of heart. Pneumogastric terminations could not be found. Heart is homogeneous, yellowish-brown, firm, and cuts with increased resistance; fibrous strands are visible here and there, and several grayish, translucent nodules are seen. The left ventricle is from 12 to 14 mm. thick; the right ventricle from 4 to 6 mm. The trabeculae are well developed. The aortic valves are distinctly thickened with numerous atheromatous patches on the ascending arch of the aorta. The mitral valve is much stenosed and thickened but without distinct nodules. The left ventricular branch of His' bundle is visible as a fan-shaped, spreading bundle. One so-called abnormal tendon fiber with very slight endocardial thickening runs to the posterior papillary muscle. No other abnormality is visible. The coronary arteries are diffusely sclerosed.

HISTOLOGICAL DESCRIPTION

The whole heart septum from the lower border of the fossa ovalis in the auricle to the apex of the ventricle was removed and cut into blocks suitable for serial section. The anterior and posterior borders were cut almost parallel to the long axis of the right ventricle with the lower portion slightly forward and the superior and inferior at right angles. One piece of tissue was cut to include Tawara's node and as much as possible of His' bundle, and sections were taken on the frontal plane. In spite of fixation in formaldehyd excellent histological detail was as a rule shown.

In the earlier sections, the muscular network of Tawara's node was found normal. Adjacent to it, beneath the endocardium of the right ventricle, were numerous swollen, vacuolated, faintly striated cells resembling Purkinje fibers. Some of these contained hemosiderin pigment granules. A small collection of plasma and small round cells were present on the edge of Tawara's node.

In later sections these small collections were found to contain many polymorphonuclear leukocytes (10 to 40 per cent). They occur both subendocardial and buried deep in fibrous or muscular tissue, usually around small vessels.

In later sections, in which the bundle was found traversing the fibrous band between the auricle and ventricle, it was approximately normal with little or no increase of fibrous tissue. The same deposits of small round cells, plasma-cells and leukocytes were found in it.

Still later the division of the bundle was shown, but the right branch could not be followed well owing to poor fixation. The left appeared in cross-section or oblique section immediately beneath the endocardium. The musculature in its upper portion, was about normal, though it also was poorly fixed. Further down, the chains of Purkinje-like cells, well separated by loose fibrous tissue from each other and from the ventricular musculature, were well shown. The cellular foci before described were also present and were much more abundant than through the ventricular muscle proper. These foci could be followed the length of the septum, with occasional extensions into the septa between the ventricular muscle bundles. The actual junction of the Purkinje fibers with the muscle-fibers was not seen. The base of the auriculoventricular valve appeared edematous and contained similar cellular foci. The valve showed no acute endocarditis. A diffuse fibrosis of considerable extent existed throughout the ventricular musculature. In places, dense fibrous masses without nuclei were found at times with a core of more fibrous tissue, and one of these occurred subendocardially directly in the path of the left branch (gumma).

Sections from Keith's node (parallel to the crista terminalis, 8 by 20 mm.) failed to reveal any abnormality, other than the inclusion of a small number of cells similar to those described above.

Histological Diagnosis.—Acute inflammation of Tawara's node and bundle of His; diffuse fibrosis and multiple gummata of ventricle.

SUMMARY

In Case 1, in which there were transient attacks of heart-block, complicated with Adams-Stokes' syndrome during the last eight days of life, there was found a marked cellular infiltration of the auriculoventricular conductive system. Furthermore, the right branch was found completely obliterated, showing that total destruction of one branch is compatible with an at times normal pulse.

In Case 2, chronic salpingitis, in a woman who sought the hospital for relief from a chronic rheumatic endocarditis with failing compensation, the hitherto localized septic process caused, three weeks after admission, a general peritonitis, pleuritis, pericarditis, and localized areas of acute myocarditis, especially in His' bundle and Tawara's node. On the day of her death, due presumably to the heart-block thus caused, there occurred four typical attacks of Adams-Stokes' syndrome, the last of which was fatal. The only other reported case that I know of in which an acute septic condition of the conducting system was associated with heart-block is that reported by Gerhardt,[7] in which a patient who had just recovered from an attack of acute articular rheumatism with temporary heart-block succumbed to typhoid fever, and at necropsy a perivascular cellular infiltration was found in His' bundle, the residuum of an acute inflammation.

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[7] Gerhardt: Deutsch. Arch. f. klin. Med., 1908, xcii, 485.

I am indebted to Drs. Riesman, Farr and Pemberton for the clinical reports and necropsy material.

THE COAGULATION OF NORMAL HUMAN BLOOD

AN EXPERIMENTAL STUDY *

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INTRODUCTION

This paper represents a study of the essential processes involved in the coagulation of blood along lines recently worked out by Bordet and Delange.[1]

This work has been carried out entirely with human blood. Nearly all the investigators in the field of coagulation of blood have worked with the blood of the lower animals. Bordet and Delange worked mostly with rabbits, somewhat with guinea-pigs and not at all with human blood. We have attempted to parallel the experiments of Bordet and Delange on rabbit's blood with experiments on human blood. We felt that such a study would not only confirm the important conclusions of Bordet and Delange but might perhaps permit a basis for deductions of clinical value. In addition we have subjected to critical study the procedures and experiments of Bordet and Delange and have attempted to carry still further the investigation of the problem of coagulation.

The literature on coagulation of blood is voluminous. Morawitz[2] in an excellent summary of the subject in 1905 gives a bibliography of 490 articles. There are many conflicting theories. The theory of Morawitz,[2,3] which is essentially identical with that of Fuld,[4,5] and the theory of Howell,[6] are perhaps the best known. Nolf,[7] Loeb[8] and DeWaele[9] are among the many who have advanced theories which differ to a greater or less extent from those of Morawitz and Howell. The whole subject has

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1. Bordet, J., and Delange, L.: Ann. de l'Inst. Pasteur, 1912, xxvi, 657. 737.

2. Morawitz, P.: Ergebn. d. Physiol., 1905, iv, 307, Parts 1 and 2.

2. Morawitz, P.: Ergebn. de Physiol., iv, Jahr. Abt. 1 and 2, 1905, p. 307.

3. Morawitz, P.: Beitr. z. chem. Phys. u. Path. (Hofmeister's), 1903, iv, 381; Deutsch. Arch. f. klin. med., 1904, lxxix, 1, 215; Handbuch der Biochemischen Arbeitsmethoden, E. Abderhalden, 1911, v, 223.

4. Fuld, E.: Zentralbl. f. Physiol., 1903, xvii, 529.

5. Fuld, E., and Spiro, K.: Beitr. z. chem. Phys. u. Path. (Hofmeister's), 1904, v, 171.

6. Howell, W. H.: Am. Jour. Physiol.. 1910, xxvi, 453; 1911, xxix, 187; 1912, xxxi, 1.

7. Nolf, P.: Arch. Internat. de Physiol., 1908, vi, 1, 115.

8. Loeb, L.: Beitr. z. chem. Phys. u. Path. (Hofmeister's), 1905, vi, 260.

9. De Waele, H.: Ztschr. f. Immunitätsforsch., 1912, xvi, 311.

been considerably complicated by the large number of terms used by the various workers. In some instances the same term is used to denote quite dissimilar substances. In other instances different workers have attributed to apparently the same substance quite divergent characteristics. The problem has been attacked from so many points of view that it is often impossible to parallel the fundamental principles of the various theories. In this paper no attempt will be made to discuss in detail the various theories.

Bordet and Delange have approached the problem of coagulation from a somewhat different angle from most of the previous work. They have used a different terminology from Morawitz, Fuld or Howell. The theory of Bordet and Delange may be simply stated as follows:

The coagulation of normal blood consists essentially of three steps;

1. Blood on being shed immediately undergoes some change which makes it quite different from the normal circulating blood and enables coagulation to ensue. Concerning this important initial step very little is known. The duration of this stage is unknown, it is probably very short. This is in agreement with practically all the theories on the subject of coagulation.

2. The second step is the formation of thrombin or the active coagulating principle of the blood. The duration of this stage can be measured and is probably the varying factor in the length of time required for coagulation. According to the theory of Bordet and Delange thrombin is formed by the reaction between cytozyme and serozyme in the presence of a soluble calcium salt.

Cytozyme in the blood is chiefly derived from the platelets, to a much less extent from the white corpuscles. Outside of the blood this active principle is found in the tissue juices. The cytozyme of Bordet and Delange is roughly comparable to Howell's thromboplastic substance and Morawitz' thrombokinase. Serozyme is a substance contained in blood-serum which unites with the cytozyme to form thrombin. Serozyme is not present as such in the circulating blood or in the oxalated plasma. Serozyme may be considered as comparable to the prothrombin of Howell and the thrombogen of Morawitz. While all workers in this field agree that thrombin is the coagulating substance which is produced in the blood, there are radical differences as to the method of the formation of thrombin and the substances used in its production.

3. The third stage is the action of the thrombin when formed on the fibrinogen of the blood changing the fibrinogen into fibrin and causing coagulation. Calcium is not required for this stage. The duration of this stage under favorable conditions is probably within two minutes. Here again practically all of the workers are agreed on the general principle of this step.

Bordet and Delange admit the possibility of the presence and the action in the first stage of an antithrombin, which plays an important rôle in the theory of Howell and the presence of which is conceded by most observers. In Howell's theory antithrombin is the substance that keeps blood fluid in the vessels and it is only by the neutralization, as it were, of antithrombin by the thromboplastic substance (the cytozyme of Bordet and Delange), that prothrombin is set free and permitted to be changed to thrombin.

COLLECTION AND PREPARATION OF THE BLOOD

In collecting and preparing the blood from human beings for these experiments, the method prescribed by Bordet and Delange based on the original technic of Mosen[10] for animals was followed with slight modification. As pointed out by those writers, it was found that the experimental results were not consistent or accurate unless the blood had been obtained under conditions which prevented the occurrence of any part of the process of coagulation during this procedure. For this reason the technic of collecting the blood will be described in detail.

The essential point in this technic is to oxalate the blood. This precipitates the calcium. By this process of decalcification the blood is rendered spontaneously incoagulable before any of the preliminary steps of coagulation have taken place. This was accomplished by taking the blood directly from the veins through a glass tube, coated with paraffin, into a paraffined flask containing a solution of sodium oxalate. Preliminary to securing the blood a small glass tube about 5 cm. long and 4 mm. in diameter and four Erlenmeyer flasks holding 150 c.c. were sterilized, dried and coated with paraffin.[11] The flasks were graduated to 100 c.c. and in each flask was placed 10 c.c. of 1 per cent. sodium oxalate solution in salt solution 0.5 to 100. The blood for these experiments was obtained from patients in the medical wards of the Massachusetts General Hospital. All the patients had essentially normal blood. The hemoglobin, cell counts and platelet counts were within normal limits. The coagulation times by the method described by Lee and White[12] were also within normal limits.

The slight operation necessary to collect the blood was done with the ordinary aseptic precautions. The arm of the patient, having been surgically prepared, is placed at right angles to the bed with the forearm resting on a small table and the median bacillic vein is exposed for about one inch under local anesthesia. The vessel is tied above and temporarily occluded below with a light artery clip or by making traction upward on a silk thread passed under the vessel. The glass tube is then inserted into the vein and secured with a ligature. Previous to this step a tourniquet is applied above the elbow, tight enough to obstruct the venous return. When the clamp is removed from the vein, the blood flows from the end of the tube with considerable pressure. After wasting the first few cubic centimeters, the blood is allowed to fall directly into the oxalate solution in the paraffined flasks until the level of the mixture reaches the 100 c.c. mark. This gives a spontaneously incoagulable blood, oxalated 1 to 1,000. With the exception of the paraffin coating of the tube and flask the blood has not been in contact with a foreign body until decalcified by the sodium oxalate solution. This oxalated blood is immediately subjected to fractional centrifugalization to separate the plasma and the cellular elements. The blood is first poured into several centrifugal tubes and whirled at a moderate rate of speed for about fifteen minutes which gives a precipitate and a supernatant fluid. The precipitate consists of a small white deposit of calcium oxalate at the bottom of the tube and a broad layer of red cells surmounted by a thin "buffy coat" of white corpuscles. Some platelets are also carried down with the red and the white cells. The supernatant fluid, which is then drawn off with a pipet, is a yellowish plasma, clouded by the platelets which for the most part have remained in suspension after moderate centrifugalization. Microscopic examination of a drop of this fluid shows that in addition to platelets, it still contains a few red and white cells. If the supernatant fluid is centrifugalized at a higher rate of speed for fifteen minutes, the red and white corpuscles which remain can be precipitated with some blood-platelets, leaving a plasma containing no cells except the platelets. This fluid, rich in platelets, is called "cloudy plasma" and will be frequently referred to as such in the subsequent experiments. The cloudy plasma is then given a second, more prolonged and rapid centrifugalization, usually about an hour with four thousand revolutions to the minute, which throws down the platelets in a tenacious clump in the bottom of the tube leaving a supernatant fluid of clear amber plasma. This is termed the "clear plasma." It still contains a few platelets which can be largely eliminated by repeating the centrifugalization for another hour. The resulting supernatant fluid which looks like the clear plasma but does not contain so many platelets is termed "very clear plasma." The number of platelets in the plasma depends on the energy of centrifugalization. The cloudy plasma has many, the clear plasma less and the very clear plasma only a few. Theoretically, it might seem possible so to prolong the centrifugalization as to free the plasma entirely of platelets. We have never been able to obtain such a plasma and this corresponds with the experience of Bordet and Delange. After a thorough washing in physiological salt solution containing 0.5:1,000 sodium oxalate, the platelets are made into a thick suspension in the same fluid. Some difficulty is experienced in breaking up the clump of sticky platelets. This can be most easily done by repeatedly drawing the platelets up into a small pipet and forcing them out through the fine point of the pipet, which rests against the bottom of a tube. After each washing the platelets are thrown down by rapid centrifugalization. Usually two or three washings are sufficient. The yield of platelets varies with the individual blood and the care with which the blood has been collected and put through the process of centrifugalization. From 200 c.c. of oxalated blood a thick suspension of platelets can usually be obtained which on standing gives a sediment of platelets about 2 cm. in depth in a tube of 7 mm. diameter. The plasma solutions obtained by this procedure, if kept in the cold, remain unaltered and suitable for experimental purposes for from four to six days. If some error has been made in the preparation a light cloud appears in the liquid. The suspension of platelets is more stable if kept in the cold and if sterilized, as described later in the paper, can be used for several months.

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[10] Mosen, R.: Arch. f. Anat. u. Physiol., Physiol. Abt., 1893, p. 352.

[11] The paraffin used in these experiments was obtained from the Bausch & Lomb Optical Company, Rochester, N. Y., and labeled "Best white imported paraffin. melting-point 45 to 50 C." (122 F.)

[12] Lee, R. I., and White, P. D.: Am. Jour. Med. Sec., 1913, cxlv, 495.

In the course of our work an effort was made to simplify the technic of collecting the blood (exposure of a vein and the use of a coated glass tube) by resorting to the usual clinical method of puncturing the vein at the elbow through the skin and drawing the blood through a needle into a paraffined vessel containing oxalate solution. This was tried on several patients and no difficulty was experienced in obtaining the blood but such blood did not give so good a yield of platelets or furnish plasma so clear or stable as was obtainable from blood taken by the other method. Even a brief contact with such foreign bodies as the metal needle and the rubber tube before the blood has been oxalated appeared to be sufficient to precipitate some of the earlier stages of coagulation. Although these reactions may not have progressed so far as actual fibrin formation, the blood is so altered that certain of the more delicate experiments can not be performed. We came to the conclusion that for experimental purposes at least it is necessary to obtain the blood by the somewhat laborious method which has been described.

In addition to cloudy plasma, clear plasma, very clear plasma and the suspension of platelets, three chemical solutions are prepared for use in the subsequent experiments.

Decalcifying Oxalate Solution, 1:100.—This is made by adding sodium oxalate in the proportion of one part to one hundred of a 0.5 per cent. salt solution. This is the stock solution which is used whenever it is necessary to oxalate the blood.

Physiological Oxalate Solution.—This solution, which is used in washing and making up the suspension of platelets, consists of physiological salt solution (0.9 per cent.) oxalated to 0.5 parts in 1,000.

Recalcifying Fluid.—This solution is made by adding 770 c.c. of salt solution to 30 c.c. of a 1:100 calcium-chlorid solution. The exact strength of this 1 per cent. calcium-chlorid solution is such that one volume will completely precipitate an equal volume of 1:100 oxalate solution. Four volumes of the recalcifying solution contains one and one-half the calcium needed to neutralize the oxalate in one volume of the plasma solution, oxalated 1 to 1,000.

Fibrinogen.—The clear oxalated plasma is used by Bordet and Delange as a solution of fibrinogen to test the coagulating power of any given solution. For this purpose they prefer the oxalated plasma to the pure fibrinogen solutions (which are made by repeatedly precipitating the fibrinogen with concentrated sodium-chlorid solutions) because it is so difficult to obtain by this method fibrinogen which is not contaminated by a trace of some one of the coagulating agents. The oxalated plasma contains in addition to fibrinogen, some elements from which cytozyme and serozyme are derived; but as will be explained later these agents are rendered inert by the excess of oxalate.

This test solution is frequently used by Bordet and Delange in the form of a diluted "monoxalated plasma" and a diluted "dioxalated plasma." The diluted "monoxalated plasma" is made by diluting the clear oxalated plasma with four volumes of a 1 to 1,000 oxalate solution. This 1:1,000 oxalate solution is made by adding one volume of a 1:100 oxalate solution to nine volumes of normal salt solution. The diluted "dioxalated plasma" is made by diluting the clear oxalated plasma with four volumes of a 2:1,000 oxalate solution which consists of eight parts of normal salt solution and two parts of a 1:100 oxalate solution.

Cytozyme.—The platelets which are obtained in the process of fractional centrifugalization are the chief source of cytozyme. This element is also found in the white corpuscles and tissue juices; but in the experiments which follow, the washed suspension of platelets is usually employed when a cytozymic action is desired.

Serozyme.—As will be demonstrated later, serozyme is found in the serum which is obtained by defibrinating the coagulated clear plasma. When freshly made this serum also contains some active thrombin. The thrombin is rapidly enfeebled by age and has almost disappeared in serum which is 24 hours old. This 24-hour old serum is used by Bordet and Delange as the serozyme solution. "Salted plasma": In addition to sodium oxalate other salts such as sodium chlorid and sodium citrate are employed to make an incoagulable plasma. Blood obtained as described above is "salted" by collecting it in a flask containing a 20 per cent. sodium-chlorid solution in such an amount that the final plasma contains 5 per cent. sodium chlorid. The red and white corpuscles are removed by centrifugalization, leaving a clear red plasma. This so-called salted plasma is spontaneously incoagulable although it contains calcium. If the proper proportion of sodium chlorid is reestablished by the addition of distilled water (four volumes) coagulation will take place in this plasma.

Our experimental studies have dealt especially with three factors in coagulation: cytozyme, serozyme and thrombin. The other two important factors in coagulation, calcium and fibrinogen, will be discussed only incidentally, since all observers are in essential agreement as to the part which they play in coagulation. The purpose of this study is to investigate the nature and action of the three substances denominated by Bordet and Delange, cytozyme, serozyme and thrombin.

In our work we have retained the terms used by Bordet and Delange. The words "cytozyme" and "serozyme" imply from their derivation the characteristics of an enzyme. We shall show later that cytozyme and serozyme do not act like enzymes.

CYTOZYME

The cytozyme of Bordet and Delange corresponds fairly closely to the thrombokinase of Morawitz and the thromboplastic substance of Howell.

According to Bordet and Delange the active principle, cytozyme, is contained in the blood-platelets, in tissue juice, and to a much less extent in the white corpuscles of the blood.

BLOOD PLATELETS AS A SOURCE OF CYTOZYME

The importance of blood-platelets in coagulation, which has been recognized since the work of Bizzozero[13] and Hayem[14] about 1880, can be demonstrated in various ways. Cloudy oxalated plasma, which is the oxalated blood centrifugalized for about fifteen minutes at low speed, will clot in from eight to fifteen minutes after the addition of recalcifying fluid. By further centrifugalization for one hour, one obtains what we call clear plasma; very clear plasma is obtained by centrifugalization for two hours. The only difference in these plasmas is their content of blood-platelets. Examination of the sediment of the centrifugalized plasma after the removal of the red blood-corpuscles shows only blood-platelets and a rare leukocyte. The average coagulation time of clear plasma is from twenty-five to thirty-five minutes. At times we have succeeded in obtaining a very clear plasma which requires forty-five minutes to coagulate on being recalcified. If blood-platelets are added, either from the same blood or from another blood, one obtains again cloudy plasma which will clot in the time of the original cloudy plasma, which is from eight to fifteen minutes. In short, the coagulation time of the recalcified oxalated plasma depends on the number of blood-platelets in the plasma. This phenomenon was first demonstrated by Mosen[10] in 1893. An illustrative protocol follows:

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[13] Bizzozero, J.: Virchows Arch. f. Path. Anat. u. Phys., 1882, lxl, 261.

[14] Hayem, G.: Du sang et de ses altérations anatomiques, Paris, 1889, p. 291.

Experiment 1.—Take four tubes, A, B, C and D; in A is 1 c.c. of oxalated cloudy plasma and 6 drops of the suspension of platelets. In B is 1 c.c. of oxalated cloudy plasma. In C is 1 c.c. of oxalated clear plasma (cloudy plasma centrifugalized one hour). In D is oxalated very clear plasma (cloudy plasma centrifugalized two hours). To each tube add 4 c.c. of the recalcifying fluid. A clots in five minutes, B in ten minutes, C in twenty-five minutes and D in forty minutes.

We have never been able to obtain a plasma which was incoagulable on recalcification by centrifugalization, no matter how prolonged. This coincides with the experience of Bordet and Delange.

If to the clear oxalated plasma, however, nine volumes of distilled water is added and a current of carbon dioxid is passed through, a turbidity appears. The plasma is then centrifugalized and clear fluid is obtained which either does not clot or clots very slowly on being recalcified and by replacing the sodium chlorid. This clear fluid will clot, however, on the addition of blood-platelets. Bordet and Delange assume that the carbon dioxid with the distilled water causes a precipitation of some substances which allows the blood-platelets to be more easily removed by centrifugalization.

Experiment 2.—To 1 c.c. of clear oxalated plasma add 9 volumes of distilled water. Pass a current of carbon dioxid through the mixture, a turbidity appears, centrifugalize energetically. Pour into Tube A 5 c.c. of the clear supernatant fluid. Into Tube B the remaining 5 c.c. after shaking. Then replace the sodium chlorid and add calcium by adding 0.2 c.c. of a 20 per cent. solution of sodium chlorid and 0.2 c.c. of a 0.5 per cent. of calcium chlorid to each tube. B clots firmly in twenty-five minutes; A shows only a moderate clot the next day.

THE SOLUBLE ACTIVE PRINCIPLE OF PLATELETS

The presence of the blood-platelets themselves is not essential to coagulation. Strong saline solutions apparently have the power of dissolving the active principle of the platelets.

Experiment 3.—If the blood is taken into a solution of sodium chlorid instead of sodium oxalate (40 c.c. of blood and 10 c.c. of 20 per cent. sodium chlorid) this plasma, the so-called "salted" plasma, is spontaneously incoagulable. But no matter how energetic or how prolonged is the centrifugalization of this plasma it clots in three to five minutes on the addition of four volumes of distilled water with 0.015 per cent. calcium chlorid.

The plasma can be microscopically demonstrated to be practically free from platelets. Therefore the actual presence of blood-platelets is not necessary for coagulation.

Bordet and Delange have shown that by heating a solution of blood-platelets in salt solution and keeping the solution for some time, they can obtain a clear supernatant fluid without blood-platelets yet causing coagulation. Howell,[6] Austin and Pepper[14] and others have shown that the active coagulating principle in the blood-platelets while essentially insoluble in normal salt solution is soluble in distilled water. We have left distilled water in contact with blood-platelets for two hours and then found that the fluid freed from the blood-platelets by centrifugalization has essentially the same effect as the blood-platelets themselves.

Experiment 4.—Five tubes, A, B, C, D and E. In each tube put 0.4 c.c. of the recalcifying fluid and 0.1 c.c. of serum (obtained the day before by defibrination of the clot formed by the mixture of 1 c.c. of clear oxalated plasma and 4 c.c. of the recalcifying fluid). To A add nothing. To B add 1 drop of the suspension of platelets. To C add 1 drop of the supernatant fluid of the suspension of platelets, kept for two weeks after heating to 100 C. for fifteen minutes. To D add 1 drop of the supernatant fluid obtained by centrifugalization of a mixture of platelets and distilled water after two hours of contact. To E add 1 drop of clear supernatant fluid obtained by centrifugalization of the suspension of platelets in normal salt solution. After fifteen minutes add 0.5 c.c. of the diluted dioxalated plasma. B, C and D coagulate in two or three minutes; A and E do not coagulate even the next day.

It is evident, therefore, that the suspension of blood-platelets, the extract of platelets in sterile water, and the heated extract in salt solution are all equally effective. But without blood-platelets or some active extract of them, there is no coagulation.

Blood-platelets alone either in thick suspension or in a solution of distilled water (with or without calcium) do not cause the coagulation of fibrinogen.

Experiment 5.—Four tubes, A, B, C and D. In Tube A, 0.5 c.c. of suspension of platelets; in Tube B, 0.5. c.c. of the suspension of platelets and 0.5 c.c. of the recalcifying fluid. In Tube C, 0.5 c.c. of solution of the platelets is distilled water. In Tube D, 0.5 c.c. of the solution of platelets in distilled water and 0.5 c.c. of the recalcifying fluid. After fifteen minutes add 0.5 c.c. of the diluted dioxalated plasma to each tube. There is no coagulation in any of the tubes.

THE QUANTITATIVE ACTION OF PLATELETS

Various observers have maintained that the action of the blood-platelets is essentially that of an enzyme, i. e., that a small amount of the active principle of blood-platelets can be used repeatedly in assisting coagulation. This is shown not to be the case by the fact cited above, that the coagulation time of the recalcified oxalated plasma varies approximately with the number of blood-platelets in the plasma. An oxalated plasma, rich in blood-platelets, coagulates in five to ten minutes on recalcification. The oxalated plasma, poor in platelets, which coagulates in thirty minutes on recalcification, coagulates in five to ten minutes on the simple addition of platelets before recalcification.

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15. Austin, J. Harold, and Pepper, O. H. P.: Experimental Observations on the Coagulation of Oxalated Plasma with a Study of Some Cases of Purpura, The Archives Int., Med., 1913, xi, 305.

The accurate measuring of the platelets in the suspension is very difficult. It is possible, however, to use suspensions of different opacities and thus to secure suspensions of different strengths. It is possible to obtain a suspension so poor in platelets that no coagulation ensues when all the other elements are added in their usual quantities.

Experiment 6.—Two tubes, A and B. In each put 0.4 c.c. of the recalcifying fluid and 0.1 c.c. of serum. Add to A 1 drop of ordinary suspension of platelets; to B 1 drop of a very thin suspension of platelets. After fifteen minutes add 0.5 c.c. of diluted dioxalated plasma. Coagulation takes place in two minutes in A; there is no coagulation in B.

It has been shown, therefore, that the platelets act in a quantitative manner, and that there is a minimum amount of platelets required to furnish sufficient thrombin to coagulate a given amount of fibrinogen.

RESISTANCE TO HEAT; PRESERVATION OF BLOOD-PLATELETS

Suspensions of blood-platelets can be heated at 100 C. for fifteen minutes without interfering with their activity in assisting coagulation. We have even exposed suspension of blood-platelets to dry heat at 120 C. for fifteen minutes and find that the blood-platelets have not lost their activity. A sterile suspension of blood-platelets maintains its activity as a factor in coagulation apparently unimpaired for several weeks.

Experiment 7.—Four tubes, A, B, C and D. In each tube is placed 0.4 c.c. of the recalcifying fluid and 0.1 c.c. of serum. To Tube A add 1 drop of the suspension of platelets. To Tube B add 1 drop of the suspension of platelets, heated at 100 C. for fifteen minutes; to Tube C 1 drop of the suspension of platelets heated to 120 C. for fifteen minutes; to Tube D add 1 drop of the suspension of platelets kept in the refrigerator for several weeks after heating to 100 C. After fifteen minutes add to each tube 0.5 c.c. of diluted dioxalated plasma. A, B and D clot firmly in two to three minutes and C clots firmly in three to five minutes.

THE RÔLE OF PLATELETS IN CLOT RETRACTION

LeSourd and Pagniez[16] and others have pointed out that blood-platelets have a remarkable effect in causing a retraction of the clot. The following typical protocol is convincing:

Experiment 8.—If clear oxalated plasma is recalcified and the clot left for several days there will be only a slight retraction of the clot. However, if to 1 c.c. of the cloudy plasma is added 30 drops of a thick suspension of platelets and then 4 c.c. of recalcifying fluid is added, coagulation takes place in about six minutes and strong retraction begins in less than an hour. The clot is retracted down at the end of two days to the size of a small almond in the midst of clear fluid. If this clot is removed and microscopic sections are made and stained by Wright's[17] method of staining blood-platelets in tissues, one sees the following typical appearance: The clot appears like some homogeneous colloid material, no fibrin threads are seen; scattered through the clot are well-preserved platelets and here and there strands of material resembling fused conglomerate platelets. Clots formed with the use of a solution of platelets do not retract.

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[16] Le Sourd, L., and Pagniez, P.: Jour. de phys. et path. gen., 1907, ix, 579.

[17] Wright, J. H.: Jour. Morphol., 1910, xxi, No. 2.

This relation of the blood-platelets to the retraction of the clot has been observed clinically by various writers besides Bordet and Delange, especially by Hayem[18] and Duke.[19] LeSourd and Pagniez[20] have recently used this property of blood-platelets as a biologic test for the presence of blood-platelets in various organs.

RED BLOOD-CORPUSCLES AS CYTOZYME

We have tried various substances to test their efficiency in replacing blood-platelets. Austin and Pepper[15] conclude from their experiments that all the corpuscular elements of the blood yielded the same active principle in assisting coagulation that is found in the blood-platelets. We feel that their technic is open to serious criticism, since our experience has shown, as we have said, that unless the most careful precautions are used blood-platelets are diffused through the whole blood. We have taken suspensions of red blood-corpuscles from the lower third of the resulting sediment obtained by the first centrifugalization of the oxalated blood. Such suspensions of red blood-corpuscles, thoroughly washed, are not effective in replacing the blood-platelets. We used very thick suspensions and as much as 10 to 15 drops of the suspension of red blood-corpuscles in contrast with 1 drop of the suspension of platelets yet no coagulation occurred. Furthermore, distilled water left in contact with the red blood-corpuscles does not show any activity in assisting coagulation.

Like the platelets, the suspensions of the red blood-corpuscles are not able of themselves to coagulate fibrinogen with or without the presence of calcium.

Experiment 9.—Five tubes, A, B, C, D and E. In A, B and C put 0.4 c.c. of the recalcifying fluid and 0.1 c.c. of serum; in D put 0.5 c.c. of the recalcifying fluid; in E, 0.5 c.c. of physiological salt solution; to A add 1 drop of the suspension of platelets; to B add several drops of the suspension of red blood-corpuscles; to C add several drops of the supernatant fluid of a mixture of distilled water and red blood-corpuscles which has been in contact for over two hours. To D and E add several drops of the suspension of red blood-corpuscles. After fifteen minutes add 0.5 c.c. of diluted dioxalated plasma. Coagulation in three minutes in A, no coagulation in B, C, D or E.

We are therefore forced to conclude that the red blood-corpuscles do not possess any activity as cytozyme.

WHITE CORPUSCLES AS CYTOZYME

Bordet and Delange injected sterile bouillon into the peritoneal cavity of guinea-pigs and obtained a fluid rich in leukocytes but containing no other cellular elements of the blood. This fluid clotted very slowly spontaneously. The addition of platelets to this fluid caused a more rapid coagulation. Bordet and Delange conclude from this experiment that leukocytes furnished some cytozyme, but to a much less degree than platelets. As we worked with human material so far as possible, we did not repeat this experiment. We are not able to obtain leukocytes from the blood without the presence of large numbers of blood-platelets. We obtained leukocytes from various sources, however. We obtained leukocytes in three cases of pleural empyema, in two cases due to the pneumococcus, and one case to the streptococcus pyogenes. We also obtained leukocytes from the urinary sediment of a case of cystitis and also from the meningeal exudate in a case of epidemic cerebrospinal meningitis.

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[18] Hayem, G.: Leçons sur les maladies du sang, Paris, 1900, p. 77.

[19] Duke, W. W.: The Pathogenesis of Purpura Hemorrhagica with Especial Reference to the Part Played by Blood-Platelets, The Archives Int. Med., 1912, x, 445.

[20] Le Sourd, L., and Pagniez, P.: Compt. rend. de sc. Par., 1913, lxxiv, 580.

Microscopical examination of this material showed in every case no formed elements except the leukocytes. The material was washed many times with normal salt solution, containing a trace of sodium oxalate, and finally suspensions of the leukocytes were made in this fluid. These suspensions corresponded in opacity to the suspension of blood-platelets. Contrary to the findings of Bordet and Delange, we were unable in parallel experiments, repeated many times, to detect any constant real difference between the activity of the platelet suspensions and that of the leukocyte suspensions. Further, the suspension of leukocytes resisted heat in a manner precisely similar to the blood-platelets. Moreover if distilled water is left in contact with leukocytes and the leukocytes are then removed by centrifugalization, we get a solution which is active in assisting coagulation. But the clots formed by the use of this suspension of leukocytes did not retract.

Experiment 10.—Five tubes, A, B, C, D and E. To each tube is added 0.4 c.c. of the recalcifying fluid and 0.1 c.c. of serum. To Tube A add 1 drop of the suspension of platelets; to tube B 1 drop of the suspension of leukocytes is added; to Tube C 1 drop of the suspension of leukocytes heated to 100 C. for fifteen minutes. To Tube D 1 drop of the clear supernatant fluid of the mixture of leukocytes with salt solution. To Tube E 1 drop of the clear supernatant fluid of the mixture of leukocytes and distilled water after contact for two hours. After fifteen minutes add 0.5 c.c. of diluted dioxalated plasma to each tube. Coagulation takes place in from two to three minutes in A, B, C and E, but does not take place in Tube D.

The leukocyte suspension seems as effective as the blood-platelet suspension in assisting coagulation.

We are aware, of course, of the objections which can be urged against the use of suspensions of leukocytes obtained in this manner. There may well be certain contaminating substances which cannot be freed from the leukocytes even by repeated washings. Nevertheless, it seems to us that the evidence is strong that in human blood the leukocytes have an action similar to that of the blood-platelets in the production of coagulation. It does not necessarily follow that the leukocytes play so important a rôle as the blood-platelets in producing spontaneous coagulation. In the first place, the platelets outnumber the leukocytes in normal blood, 50 to 1. Again it is a well-known fact that platelets rapidly gather in large numbers at any break in continuity of the vessel walls. Moreover, the peculiar adhesive property of the platelets may well be an important factor.

It has been shown by Delezenne[21] and others that birds' blood which contains no blood-platelets can be kept spontaneously incoagulable if uncontaminated by tissue juice. On the addition of foreign bodies coagulation usually takes place. Morawitz is inclined to believe that the leukocytes contain some substance that assists in coagulation but that it is not so readily available as the similar substance in the blood-platelets. Consequently, until the addition of foreign bodies to the bird's plasma no coagulation takes place.

TISSUE JUICE AS CYTOZYME

The striking effect of tissue juice on coagulation has been recognized since the work of Buchanan[22] in 1845. Following Bordet's experiments we used three specimens of muscle from human beings, three specimens of beef muscle, one specimen of lamb muscle, one specimen of rabbit muscle and one specimen of guinea-pig muscle. Each specimen of muscle was macerated in a mortar with a small amount of physiological salt solution with 0.05 per cent. sodium oxalate. The emulsion was strained through a fine wire mesh. The microscopic examination of this emulsion showed the presence of blood in a few instances. In those instances one cannot be sure of the absence of blood-platelets. Moreover, it is well known that blood platelets tend to clump and stick to the finer capillaries of muscles and the organs after death. It is doubtful even if prolonged perfusion of muscle or of an organ can entirely eliminate the possibility that the blood-platelets are still present.

Using this emulsion of muscles in drop doses, parallel experiments were undertaken to test the relative efficiency of these muscle suspensions in replacing the suspension of blood-platelets. We found that all the suspensions of muscles from various animals were effective in assisting coagulation. The results were not entirely constant but it seemed to be generally true that in the preparations made up with the suspension of human muscle, coagulation took place in practically the same time as when we used the preparation of blood-platelets. There was often a delay of a minute or two (four or five minutes as compared with two or three minutes) when the suspensions of muscle from beef, lamb, rabbit and guinea-pig were used. It was also found that in order to produce thrombin the suspension of muscles required a longer time of contact with the various other necessary elements than was required of the blood-platelets (nine to fifteen minutes compared with seven minutes).

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[21] Delezenne, C.: Arch. de physiol., 1897, ix, 333, 347.

[22] Buchanan, A.: Proc. Phil. Soc. Glasgow, 1845, ii, 16.

The suspensions of human muscle resisted heating in exactly the same way as did the suspensions of blood-platelets and the suspensions of leukocytes. These suspensions of human muscle could be heated to 100 C. for fifteen minutes without injury. On the other hand the suspensions of the various non-human muscles became inactive when heated at 100 C. for fifteen minutes. Bordet and Delange working with rabbits found that the suspension of the beef muscle when heated at 100 C. for fifteen minutes was only slightly less effective than the suspension of rabbit's muscle or the suspension of rabbit's platelets, heated in a similar manner.

Experiment 11.—Take seven tubes, A, B, C, D, E, F and G, to each add 0.4 c.c. of recalcifying fluid and 0.1 c.c. of serum. To A add nothing. To B add 1 drop of suspension of platelets, to C add 1 drop of suspension of platelets heated to 100 C., for fifteen minutes. To D add 1 drop of suspension of human muscle; to E add 1 drop of the suspension of human muscle heated to 100 C. for fifteen minutes. To F add 1 drop of suspension of beef muscle; to G add 1 drop of suspension of beef muscle heated at 100 C. for fifteen minutes. After twenty minutes add to each tube 0.5 c.c. of diluted dioxalated plasma. There is no coagulation in A to which no cytozyme has been added. Coagulation takes place in four minutes in B and C, D and F; in eight minutes in E. In G there is no coagulation in four hours but there is a clot the next day. Similar experiments were done with the muscle suspensions of lamb, rabbits and guinea-pigs. These experiments seemed to show that unheated muscle suspension can act as cytozyme, but the heated muscle suspension, except human, have very little action.

This same result can be shown in another way:

Experiment 12.—Take seven tubes, A, B, C, D, E, F and G. To each add 0.3 c.c. of clear oxalated plasma; to A add nothing. To B add one drop of the suspension of platelets. To C add 1 drop of the suspension of platelets heated at 100 C. for fifteen minutes. To D add 1 drop of the suspension of human muscle. To E add 1 drop of the suspension of human muscle heated at 100 C. for fifteen minutes. To F add 1 drop of the suspension of beef muscle. To G add 1 drop of the suspension of beef muscle heated to 100 C. for fifteen minutes. Add to each 1.2 c.c. of the recalcifying fluid. A clots in twenty-four minutes, B and C in eight minutes, D in five minutes, E in eleven minutes, F in twelve minutes and G in eighteen minutes.

Therefore it appears that the addition of the heated suspension of beef muscle hastened coagulation very little, while the other suspensions acted like the suspension of platelets.

Bordet and Delange found the muscle suspensions from animals other than the rabbit, hastened coagulation somewhat, but not so much as the suspension of rabbit's muscle. The result was the same whether the suspensions had been heated or not. They assume a certain amount of specificity in the action of cytozyme. The problem of the specificity of the different constituents which take part in coagulation is much confused. Additional evidence has been introduced by Loeb[8] and

Muraschew[23] which tends to confirm the existence of a certain amount of specificity in the reaction between some of the components of thrombin. Bordet and Delange worked, of course, with material from rabbit blood. To assume that the cytozyme of non-human muscle fails to withstand heating like human muscle because of a specificity in the cytozyme, is very attractive, yet we are not sure that this assumption is warranted. The specimens of the human muscle, obtained in two instances at necropsy, and in one instance from operation, were used very promptly. The preparation of the other muscles was generally delayed several hours at least for unavoidable reasons. There is, then, the factor of the age of the preparations as well as the factor of the different methods of death. Both these factors must be considered. We found no tendency of the muscle suspensions to cause retraction in the clot. Furthermore, as in the case of blood-platelets, neither the suspension of leukocytes nor the suspension of muscle, no matter in what quantity, would of itself cause coagulation of the fibrinogen solution either with or without the presence of calcium.

PEPTONE AS CYTOZYME

Bordet and Delange were able to substitute an emulsion of peptone for the platelet suspension. This emulsion of peptone was effective only when it was of a certain reaction. Of course, peptone is merely digested tissue. We are not aware of the exact method of preparation of the peptone used by Bordet and Delange. We have tried various forms of peptone, Witte's and Merck's peptones and Peptone "Roche." We have tried various degrees of acidity and alkalinity. With the use of Witte's peptone and Merck's peptone the preparations showed a very slight coagulum the next day, while the control showed nothing. Peptone "Roche," which is not made from animal tissue, did not show even this slight activity. We believe that this discrepancy between our findings and those of Bordet and Delange is due to the method of preparation of the peptone. We do not feel that this is an essential part of the work of Bordet and Delange. It seems probable that a peptone prepared under the most favorable conditions, especially in regard to heat, might well give the results obtained by Bordet and Delange. It is of interest, however, that our peptones which were obtained from beef, and in the preparation of which heat was used, gave with the other elements of human blood results similar to those obtained by using a heated emulsion of beef muscle.

Bordet and Delange[24] in a more recent paper have studied further the nature of cytozyme. They have been able to isolate an active principle from muscle juice and from the platelets. This active principle, which can be used in very small quantities as cytozyme, resembles a lipoid and seems to be identical with the lecithin of the muscle and platelets. We have not attempted to confirm these findings, which coincide with the work of Howell,[25] Zak[26] and others.

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[23] Muraschew: Deutsch. Arch. f. klin. med., 1904, lxxx, 187.

[24] Bordet, J., and DeLange, L.: Ann. de l'Inst. Pasteur, 1913, xxvii, 341.

SUMMARY OF OUR WORK ON CYTOZYME

From our experiments we have been able to confirm most of the work of Bordet and Delange.

We have confirmed the importance of blood-platelets in the process of coagulation. We have studied certain properties of the activity of the platelets. We have shown that *in vitro* leukocytes and tissue juice can replace platelets in the process of coagulation, and have similar properties as the platelets. We have also observed certain results that suggest that the active principle of the tissue juices has a certain amount of specificity in its action.

We find the following discrepancies between our work and that of Bordet and Delange. Human blood-platelets keep their activity even after heating at 120 C. for fifteen minutes.

We find that, *in vitro,* leukocyte suspensions seem to be as active as platelets instead of much less active, as Bordet and Delange found.

We find also, with human blood, that suspensions of muscle other than human lose their activity on heating at 100 C. for fifteen minutes.

We were unable to repeat the work of Bordet and Delange with peptone as cytozyme; this is probably due to the difference of the peptone used.

In addition to the experiments of Bordet and Delange, we have studied the red blood-corpuscles as cytozyme and found that they possess no coagulating acivity.

SEROZYME

Bordet and Delange use the word "serozyme" to denote that substance in the serum which under certain conditions unites with the cytozyme of the platelets to furnish thrombin. Serozyme may be considered as roughly comparable to the thrombogen of Morawitz and the prothrombin of Howell. Yet serozyme is far from being identical with thrombogen or prothrombin.

PREPARATION AND DEMONSTRATION OF SEROZYME

Bordet and Delange find this active principle, serozyme, best in the serum resulting from the defibrination of the recalcified clear oxalated plasma. The exact procedure follows:

Experiment 13.—One c.c. of clear oxalated plasma plus 4 c.c. of the recalcifying fluid clots in approximately thirty minutes. The clot is removed by defibrination and the resulting serum is kept for twenty-four hours and then is the substance used as serozyme. Take two tubes, A and B; in each place 0.4 c.c. of the recalcifying fluid and 1 drop of the suspension of platelets. To A add nothing; to B add 0.1 c.c. of the serum. After fifteen minutes add to both tubes 0.5 c.c. of the diluted dioxalated plasma; firm coagulation takes place in Tube B; there is no coagulation in A.

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[25] Howell, W. H.: Am. Jour. Physiol., 1912, xxxi, 1.

[26] Zak, E.: Arch. f. exper. Path. u. Pharmakol., 1912, lxx, 27.

It is evident, then, that the serum furnishes some substance which is essential for coagulation, for without this serum no coagulation takes place.

But cumulative evidence shows the substance which is called serozyme either does not exist as such in the blood-vessels or at least it cannot enter into reaction as an element in producing coagulation. Furthermore, serozyme does not exist as such in an available form even in the oxalated plasma.

Experiment 14.—Three tubes, A, B and C, contain each 0.4 c.c. of the recalcifying fluid and 1 drop of the suspension of platelets. To A add nothing; to B add 0.1 c.c. of old serum; to C add 0.1 c.c. of clear oxalated plasma. After fifteen minutes add 0.5 c.c. of the diluted dioxalated plasma; firm coagulation takes place in two minutes in B; there is no coagulation in A or C.

It can be assumed, then, that the oxalated plasma cannot be used as serozyme, yet the absence of serozyme in the oxalated plasma can also be shown by the following experiment:

Experiment 15.—The serum is obtained in the usual way the day before by the defibrination of the clot formed by the mixture of 1 c.c. of clear oxalated plasma and 4 c.c. of the recalcifying fluid. One c.c. of this serum is mixed with 9 c.c. of the recalcifying fluid and is distributed in tubes of quantities of 0.5 c.c. One drop of the suspension of platelets is added to each tube; then at minute intervals after the addition of the suspension of platelets, 0.5 c.c. of the diluted dioxalated plasma is added. In a similar manner 1 c.c. of the clear oxalated plasma is mixed with 9 c.c. of the recalcifying fluid and is likewise rapidly (to avoid coagulation) distributed into the tubes in quantities of 0.5 c.c. and 1 drop of the suspension of platelets added. At minute intervals 0.5 c.c. of the diluted dioxalated plasma is added. We have here used serum and the recalcified oxalated plasma as serozyme under identical conditions. The addition of the diluted dioxalated plasma precipitates the calcium and prevents the formation of any more thrombin. The serum mixture after contact with the platelets for less than five minutes shows no coagulation. After contact from five to ten minutes there is slight coagulation in ten to twenty minutes. Firm coagulation in three minutes is obtained after the serum mixture has been in contact with the platelets over ten minutes. With the plasma mixture, however, there is no coagulation until the plasma mixture has been in contact with the platelets for fifteen minutes, when firm coagulation takes place in ten minutes.

It is evident that the serozyme is not present as such or in available form in the oxalated plasma.

These results can perhaps be best interpreted in the following way: There exists in the blood and in the oxalated plasma an antecedent substance of serozyme which Bordet and Delange call proserozyme. In the first step in coagulation the proserozyme is either changed to serozyme or somehow becomes available as serozyme; then the process of coagulation follows.

THE EFFECT OF HEAT ON SEROZYME

The active principle of serozyme in serum is destroyed by heating at 56 C. for one-half hour. This is in marked contrast to the cytozyme.

Experiment 16.—Two tubes, A and B, contain 0.4 c.c. of the recalcifying fluid and 1 drop of a suspension of platelets. To A add 0.1 c.c. of twenty-four-hour-old serum. To B add 0.1 c.c. of twenty-four-hour-old serum which has been heated at 56 C. for one-half hour. After fifteen minutes add 0.5 c.c. of diluted dioxalated plasma. Firm coagulation takes place in A in two to three minutes; there is no coagulation in B.

The antecedent substance of serozyme in the oxalated plasma is likewise destroyed by heating at 56 C. for one-half hour, as seen in the following experiment:

Experiment 17.—Heat several cubic centimeters of clear oxalated plasma for one-half hour at 56 C. The fibrinogen is precipitated. To 1 c.c. of this heated oxalated plasma one adds 4 c.c. of the recalcifying fluid, but there is no coagulation. The same clear oxalated plasma without heat coagulates in thirty minutes on recalcification. Take two tubes, A and B, to each add 0.3 c.c. of the recalcifying fluid and 1 drop of platelets. To Tube A add 0.2 c.c. of the recalcified heated plasma, to tube B add 0.2 c.c. of twenty-four-hour-old serum. After twenty minutes add 0.5 c.c. of diluted dioxalated plasma; coagulation takes place in two to three minutes in Tube B and there is no coagulation even the next day in Tube A.

THE EFFECT OF BARIUM SALTS ON SEROZYME

Serozyme is absorbed by the action of barium sulphate, and serum treated with barium sulphate is rendered incapable of reacting with platelets. The following is a typical protocol:

Experiment 18.—Take two tubes, A and B, each of which contains 1 c.c. of serum; to A add 6 drops of a thoroughly washed suspension of barium sulphate in physiologic salt solution. To B add 6 drops of physiologic salt solution. After contact for one-half hour, centrifugalize A and pour off the supernatant fluid; then take two tubes, C and D, both containing 0.4 c.c. of the recalcifying fluid and one drop of platelets. To C add 0.1 c.c. from Tube A; to D add 0.1 c.c. of Tube B; after fifteen minutes add 0.5 c.c. of a diluted dioxalated plasma. Tube D coagulates promptly in nine minutes; in Tube C there is no coagulation even after four hours.

Barium salts also absorb the antecedent substance of serozyme in the oxalated plasma.

Experiment 19.—Mix together 30 drops of a thick suspension of barium sulphate in physiologic salt solution, 4 c.c. of the recalcifying fluid and 1 c.c. of clear oxalated plasma. After contact for several hours centrifugalize and decant. The decanted fluid is spontaneously incoagulable plasma containing all the essentials for coagulation except serozyme. This plasma will clot on the addition of serum. Take three tubes, A, B and C, each containing 1 c.c. of the plasma, recalcified and treated with barium; to Tube A add 3 drops of the suspension of platelets; to Tube B add 0.2 c.c. of serum. To Tube C add 0.2 c.c. of serum and 3 drops of platelets. There is no coagulation in Tube A; Tubes B and C clot in about eleven minutes.

Therefore, it may be assumed that barium has a selective action for serozyme and the antecedent substance of serozyme. Once thrombin has been formed, barium has no deterient effect in the process of coagulation.

QUANTITATIVE ACTION OF SEROZYME

Serozyme cannot be used repeatedly in the fashion of an enzyme. This is well shown in the following experiment:

Experiment 20.—Take four tubes, 1, 2, 3 and 4; in Tubes 1 and 2 put 0.6 c.c. of the recalcifying fluid; to Tubes 1 and 2 add 0.4 c.c. of serum. To Tubes 3 and 4 add 0.8 c.c. of the recalcifying fluid and 0.2 c.c. of serum. To Tubes 2 and 4 add 2 drops of any inert substance as physiological salt solution. To Tubes 1 and 3 add 2 drops of the suspension of platelets. After contact over night, the next day the tubes containing the platelets are centrifugalized and the supernatant fluid is drawn off. The fluid in each of the four tubes is divided into equal parts thus giving eight tubes. To one set of four tubes add 1 drop of a thin suspension of platelets, to the other set of four tubes add 1 drop of some inert solution as physiologic salt solution. After contact for fifteen minutes test the coagulating power of the fluid by adding equal amounts of the diluted dioxalated plasma to each of the eight tubes. Coagulation takes place in less than ten minutes in Tubes 2 and 4, to which the platelets were recently added. In Tubes 1 and 3, both with and without new platelets, there is no coagulation until the next day. This is due to the fact that the serozyme had all been used up to form thrombin and there was no remaining serozyme to unite with the recently added platelets to form new thrombin. The coagulation that takes place the next day is due to the feeble thrombin still remaining after being kept over night. In Tubes 2 and 4, which had no platelets, there is of course no coagulation. Therefore it may be argued that serozyme is used up in the production of thrombin and cannot be used again. One also sees in this experiment a fact which has been mentioned before, but which will be dealt with in more detail under the heading of thrombin, namely, that thrombin largely disappears in a given fluid at the end of twenty-four hours. This disappearance of thrombin in twenty-four hours is the reason that serum is kept for twenty-four hours before being used as serozyme. A recent serum, as will be shown, contains a considerable amount of thrombin; this has largely disappeared at the end of twenty-four hours. It is also evident that the more thrombin is formed the more platelets and the more serozyme is used up. It will be shown later that a plasma, rich in platelets, furnishes more thrombin and therefore uses up more serozyme.

Consequently, to obtain a serum yielding the largest amount of serozyme, it is necessary to recalcify the oxalated plasma which has been subjected to a very prolonged centrifugalization, and is on that account very clear and very poor in platelets. The serum obtained from the defibrination of the clot in the recalcified, very clear, oxalated plasma is poor in thrombin and rich in serozyme.

We have shown before that serozyme once used cannot be used again. It is possible to show further that the action of serozyme is a definitely quantitative action. With a given amount of calcium and platelets, a certain amount of serozyme is required in order that thrombin may be formed to coagulate fibrinogen. In rabbits, Bordet and Delange found that the minimum amount of serum containing active serozyme that would react with one drop of the suspension of platelets in 0.4 c.c. of recalcifying fluid and clot 0.5 c.c. of diluted dioxalated plasma was between 0.01 c.c. and 0.02 c.c. In our work on human blood we found that the minimum amount of serum required was between 0.04 and 0.08 c.c. A typical protocol is given:

Experiment 21.—A tube containing 0.04 c.c. of serum plus 1 drop of the suspension of platelets, plus 0.5 c.c. of the recalcifying fluid and left in contact for fifteen minutes and then 0.5 c.c. diluted dioxalated plasma is added. There is no coagulation. If, however, instead of 0.04 c.c. of serum 0.08 c.c. is added and the experiment repeated there is firm coagulation in four minutes.

The amount of serum required to furnish this minimum amount of serozyme depends of course on the content of the serum in serozyme. We have been able to show that the twenty-four-hour-old serum contains varying amounts of serozyme depending largely on the method of preparation. This will be dealt with in more detail under the heading of thrombin. An illustrative protocol follows:

Experiment 22.—One obtains from four different plasmas, four serums as follows: Serum A is obtained from the defibrination of a clot of the recalcified cloudy plasma which has been reinforced by the addition of several drops of platelets. Serum B is obtained from the defibrination of the clot from recalcified cloudy plasma. Serum C from the recalcified clear plasma; Serum D from the recalcified very clear plasma. The next day dilute each of these four serums with the recalcifying solution, 1 : 5, 1 : 10, 1 : 20 and 1 : 50. Then take 0.5 c.c. of each dilution of each of the four serums in separate tubes; add to each tube 1 drop of the suspension of platelets and then fifteen minutes later add 0.5 c.c. of the diluted dioxalated plasma. One finds that there is no coagulation in any of the tubes with the dilutions of 1 : 50. The quantity of serozyme is not enough in any of the serums. Serum A and Serum B do not cause coagulation in dilutions of 1 : 10 or 1 : 20. Serum A causes coagulation in one hour in dilutions of 1 : 5; Serum B in forty-five minutes. On the other hand Serum C will cause coagulation in the dilution of 1 : 5 in three minutes; 1 : 10 and 1 : 20 in ten minutes. Serum D causes coagulation in three minutes in dilutions of 1 : 5, 1 : 10 and 1 : 20. Therefore it is evident that Serum D is much more rich in serozyme and that the serum is capable of assisting in coagulation even in high dilutions.

It is evident that the more platelets in the original plasma, the more serozyme is used up to form thrombin, and the less serozyme is left in the serum after coagulation. This experiment illustrates particularly well the varying strengths of serozyme in the same amount of serum obtained under different conditions, and the importance of using, for recalcification, very clear oxalated plasma, which is very poor in platelets, in order to obtain serozyme.

SEROZYME IN NORMAL HUMAN SERUM

We have also studied somewhat human serum obtained in the usual way and allowed to clot spontaneously. Human serum, after twenty-four hours, shows comparatively little serozyme. Specimens vary, but no specimen showed coagulation in less than one-half hour, though we used amounts as high as 0.5 c.c. of serum with one drop of platelets and 0.5 c.c. of the recalcifying fluid, left in contact for fifteen minutes, and then 1 c.c. of diluted dioxalated plasma added. The obvious deductions from these observations is that in normal blood the relative proportions of serozyme and platelets are such that the serozyme is almost entirely used up in the formation of thrombin. Consequently, the serum left after the coagulation of blood contains very little serozyme.

SEROZYME IS ATTACHED TO A GLOBULIN

We have studied further the active principle in serum in an attempt to identify it more closely than has been done by Bordet and Delange and other observers. If serum twenty-four hours old is placed in a dialyzer and dialyzed over night in running water, there results a heavy white precipitate. The remaining clear supernatant fluid which one obtains by filtration can be demonstrated to contain serum albumin. In this supernatant fluid no substance which is active in any of the stages of coagulation can be demonstrated. On the other hand, if the precipitate is carefully washed on a filter with a large amount of distilled water and then taken up with a volume either of normal salt solution or of recalcifying fluid sufficient to make up the original volume, this fluid can be shown to possess a similar substance as active as serozyme in approximately the same strength. In other words the precipitate of the dialyzed serum taken up in salt solution seems to contain the same active principle as the original serum. Furthermore, the supernatant fluid of the dialyzed serum seems to contain no serozyme and none of any of the other factors active in the process of coagulation. This observation seems to link this active principle serozyme to the globulins.

SUMMARY OF OUR WORK ON SEROZYME

1. Without serozyme no coagulation takes place.
2. Serozyme is not present as such or in an available form in the circulating blood or in the oxalated plasma.
3. It is best obtained from the serum of the recalcified "very clear" plasma.
4. Serozyme is destroyed by heat at 56 C. for one-half hour.
5. It is absorbed by barium salts.
6. Serozyme does not act as enzyme and a certain minimum amount is required to have any action in a given experiment.
7. Serozyme is probably attached to the globulins of the blood since it can be demonstrated in equal potency in the precipitated globulins of serum as in the original serum. Apparently no serozyme is attached to the serum albumins.

THROMBIN

Since the work of Alexander Schmidt,[27] the view that coagulation is brought about by some active coagulating agent which is not present in the circulating blood, has been generally held. Schmidt called this agent "fibrin-ferment" and believed it to be a true ferment. Morawitz believes that there is much evidence in favor of the fermentative action of this substance, which he calls also fibrin-ferment. This substance is called thrombin by Howell and by Bordet and Delange; it is not considered by these workers to be a ferment.

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[27] Schmidt, A.: Die Lehre von den fermentativen Gerinnungserscheinungen, Dorpat, 1876.

In confirmation of the work of Bordet and Delange on rabbits' blood, it has been shown before that thrombin is similarly produced in human blood by the union of two active principles (cytozyme and serozyme) in the presence of soluble calcium salt. Thrombin is the active coagulating agent, and so far as is known, the fibrinogen of blood never coagulates without the agency of thrombin. Bordet and Delange have not isolated the active principle thrombin. It has been isolated by Howell in a somewhat complicated manner. The study of thrombin and its characteristics is somewhat difficult, as it is not present except by the action of serozyme and cytozyme, and furthermore, under ordinary conditions, thrombin rapidly deteriorates.

RAPID DETERIORATION OF THROMBIN

It can be shown that thrombin is present in excess under the usual conditions of spontaneous coagulation. Oxalated plasma, rich in platelets, when recalcified, and salted plasma, when diluted, both develop a greater amount of thrombin than is necessary merely to coagulate the fibrinogen present.

This excess of thrombin, however, rapidly disappears, and after twenty-four hours is present in so small quantities that it can no longer be regarded as an important factor.

This is shown on the following experiment:

Experiment 23.—Five tubes, A, B, C, D and E. Tube A contains 1 c.c. of salted plasma; Tube B 1 c.c. of cloudy oxalated plasma to which additional platelets have been added. Tube C contains 1 c.c. of cloudy oxalated plasma; Tube D contains 1 c.c. of clear oxalated plasma. Tube E contains 1 c.c. of very clear oxalated plasma. To Tube A is added 4 c.c. of distilled water with 0.015 per cent. calcium chlorid; to Tubes B, C, D and E is added 4 c.c. of the recalcifying fluid. Tube A clots in four minutes, Tube B clots in four minutes, Tube C in ten minutes, Tube D in thirty minutes and Tube E in forty minutes. As soon as a firm clot has formed it is defibrinated and one gets Serum A, Serum B, Serum C, Serum D and Serum E. These serums are then tested for thrombin at varying intervals. One mixes equal parts of each serum and diluted, dioxalated plasma; one finds in the case of Serum A that absolutely fresh serum will clot diluted dioxalated plasma in four or five minutes. One hour later this same Serum A requires seven or eight minutes to clot the same amount of the fibrinogen solution. Serum A when twenty-four hours old will form only a feeble clot after twelve hours' contact with the fibrinogen solution. Serum B will clot when fresh an equal amount of the fibrinogen solution in thirty minutes; Serum C when fresh in one hour, Serum D when fresh in five hours, Serum E when fresh in ten hours. These last four serums when kept over night will only show a feeble clot after contact for more than twelve hours with the fibrinogen solution. It is evident therefore that thrombin thus obtained deteriorates rapidly and after twenty-four hours is almost absent. The serum obtained from blood which has been allowed to clot spontaneously shows the same characteristics. The fresh serum will clot an equal amount of the fibrinogen solution in twenty minutes to one hour. Serum which is twenty-four hours old requires over ten hours to produce a feeble clot in an equal amount of the fibrinogen solution.

THE EFFECT OF VARIOUS SALTS ON THROMBIN

It has long been known that various salts when added to blood prevent coagulation. We have shown above that barium salts interfere with the process of coagulation by their influence on serozyme.

THE EFFECT OF CONCENTRATED SODIUM CHLORID SOLUTION ON THROMBIN

It has already been shown that a sufficiently strong mixture of sodium chlorid and blood will not coagulate. We have also shown that in this mixture coagulation takes place when the salt content is reduced to that of an approximately physiologic salt solution. The serum resulting from the defibrination of the clot contains a large amount of thrombin. Such a serum (as has been shown) contains more thrombin than the serum from the clot which results from the recalcification of oxalated plasma. As will be shown later, this difference is partly due to the harmful effect of the oxalate solution on thrombin. But the difference is probably largely due to the diffusion of the active principle of the platelets in concentrated salt solution, as was shown under the discussion of cytozyme. It is evident, then, that no permanent damaging effect on thrombin or any of its necessary constituents is brought about by the concentrated saline solution. This can also be shown as follows:

Experiment 24.—To two tubes, A and B, add 0.2 c.c. of a 10 per cent. solution of sodium chlorid with four times as much calcium chlorid as is present in the recalcifying fluid. To Tube B add 1.8 c.c. of distilled water. Add to both A and B 0.4 c.c. of serum and 3 drops of platelets. After forty minutes add to A 1.8 c.c. of distilled water and immediately to both A and B 1.5 c.c. of diluted dioxalated plasma. In Tube A in which the mixture of serum and platelets was brought in contact with a concentrated solution of sodium chlorid there is no coagulation. The contact was sufficiently long and just before the fibrinogen solution was added the sodium chlorid solution was restored to the usual physiologic strength. In Tube B coagulation takes place in eight minutes.

We can therefore assume that concentrated solutions of sodium chlorid prevent the formation of thrombin, although all the necessary constituents are present. Just how the concentrated solution of sodium chlorid acts is not apparent.

EFFECT OF CITRATE SOLUTIONS ON THROMBIN

Solutions of sodium citrate prevent the formation of thrombin, as is shown in the following experiment:

Experiment 25.—If 0.2 c.c. of oxalated plasma and 0.1 c.c. of sodium citrate solution 4 per cent. and 0.8 c.c. of the recalcifying fluid are mixed together there is no coagulation. Furthermore, one takes four tubes and each contains 0.3 c.c. of the recalcifying fluid and 0.2 c.c. of serum. To Tube A 0.1 c.c. of sodium citrate solution 2 per cent. is added. To Tubes C and D 0.1 c.c. of physiologic salt solution is added. Add a drop of the suspension of platelets to Tubes A, B and C. After fifteen minutes add to Tube B 0.1 c.c. of the 2 per cent. sodium citrate solution and add to all four tubes 0.5 c.c. of diluted dioxalated plasma. Coagulation takes place in less than two minutes in Tubes B and C, but there is only feeble coagulation after twelve hours in Tubes A and D. To Tube D no platelets were added and to Tube A the citrate solution was added with the serozyme and cytozyme. In Tube B the citrate solution was added after the formation of the thrombin and coagulation takes place rapidly. Therefore solutions of citrate prevent the formation of thrombin but do not exert any influence on the coagulating power of thrombin already formed.

EFFECT OF OXALATE ON THROMBIN

Oxalate solutions prevent the formation of thrombin by precipitation of calcium salts. Thrombin once formed does not require the presence of calcium in order to coagulate fibrinogen solutions. This has been shown repeatedly. The fibrinogen solution contains sufficient oxalate so that the calcium in the usual solution in which the thrombin is formed is all precipitated and there is an excess of oxalate. On the other hand, there is evidence that coagulation takes place more rapidly if there is a slight amount of free and available calcium when the initial contact takes place between thrombin and the fibrinogen solution.

Furthermore, the presence of oxalate seems to have a harmful effect on thrombin. Bordet and Delange utilized these two facts in the procedure of separate oxalation. The principle of this procedure is the precipitation of the calcium by oxalate after the formation of thrombin, and then, after five minutes' contact between the excess of oxalate and thrombin, the addition of the fibrinogen solution in the form of diluted monoxalated plasma. The proportions used are such that the total amount of oxalate is precisely the same as in the case of the use of the diluted dioxalated plasma as a fibrinogen solution. The only difference is the precipitation of the calcium before the contact between thrombin and fibrinogen. This method is especially sensitive in demonstrating a contrast between fresh active thrombin and an old feeble thrombin. When thrombin is fresh, active and abundant, the fact that it contains no soluble calcium salt when it comes in contact with the fibrinogen solution makes no difference. There is, however, a striking contrast in the case of an old relatively feeble and scanty thrombin. An illustrative protocol follows:

Experiment 26.—Fresh thrombin is obtained by defibrinating the clot of the diluted salted plasma. Take parallel tubes and test equal parts of this serum against an equal part of the diluted dioxalated plasma and also against equal parts of the diluted monoxalated plasma, having in the last instance oxalated the serum, 1 : 1,000. The serum is tested when fresh and at the end of an hour. The fresh serum in each instance causes coagulation in from two to three minutes. At the end of an hour the serum tested against an equal amount of diluted dioxalated plasma requires seven or eight minutes for coagulation. By the method of separate oxalation one to two hours is required.

The rapid deterioration of thrombin and the further weakening of the action of old thrombin by exposing it to oxalate solution and decalcifying it before bringing it in contact with fibrinogen is also shown in the following experiment, in which thrombin is prepared somewhat differently.

Experiment 27.—Many tubes of thrombin are prepared by mixing 0.4 c.c. of the recalcifying fluid, 0.1 c.c. of serum and 1 drop of the suspension of platelets. The thrombin is then tested against 0.5 c.c. of the diluted dioxalated plasma and also by the addition of 0.1 c.c. of sodium oxalate solution, 0.5 per cent, and five minutes later of 0.5 c.c. of diluted monoxalated plasma. The tests are made at varying times. Coagulation under four minutes takes place in the mixtures to which the diluted dioxalated plasma is added until the thrombin is ten hours old. Thrombin twenty-four hours old, requires over twelve hours to cause a feeble clot in the diluted dioxalated plasma. In the method of separate oxalation, thrombin up to two hours old requires less than four minutes to clot the fibrinogen solution. The time is gradually lengthened and thrombin twenty-four hours old will cause no coagulation in the method of separate oxalation.

THROMBIN AND SEROZYME IN SERUM

It has been shown that serum twenty-four hours old contains very little thrombin. It is this twenty-four-hour old serum that is used as serozyme. The relation between thrombin and serozyme in serum is interesting. We have shown that both cytozyme and serozyme act in a quantitative manner. It follows, therefore, that in a given blood or plasma with only a given amount of the antecedent substance of serozyme, the more thrombin that is formed from the reaction between the cytozyme and the serozyme the less serozyme will be available in the serum after coagulation and separation of the serum. Therefore, the more thrombin a serum contains the less serozyme is available. This can be well tested experimentally if one controls the amount of thrombin by using varying amounts of platelets. It follows that the fewer available platelets there are to react to form thrombin, the less thrombin will be formed and the more serozyme will remain in the serum. This is well shown in the following experiment:

Experiment 28.—A is oxalated cloudy plasma to which several drops of a thick suspension of platelets have been added. B is oxalated cloudy plasma; C is clear oxalated plasma, D is a very clear oxalated plasma, obtained by prolonged centrifugalization at high speed. One c.c. of each of these plasmas is recalcified by the addition of 4 c.c. of the recalcifying fluid. After coagulation the clot is removed by defibrination and one has Serum A, Serum B, Serum C and Serum D. Each of these serums is diluted one to five and tested for thrombin against an equal volume of diluted dioxalated plasma. A clots in three hours, B in five hours, C in twelve hours and D in twenty four hours. Therefore thrombin is demonstrated to be present in proportion to the amount of platelets used. On the next day Serum A, Serum B, Serum C and Serum D are each diluted with the recalcifying fluid 5 times, 10, 20 and 50 times. Then prepare tubes as follows: Take 0.5 c.c. of each dilution of each serum in separate tubes; to each add 1 drop of suspension of platelets and fifteen minutes later 5 c.c. of diluted dioxalated plasma. The tubes containing Serum D in dilutions of 1 : 5, 1 : 10 and 1 : 20 clotted in two minutes. There was no clot in the dilution 1 : 50 even the next day. The tubes containing Serum C clotted in less than five minutes in dilutions 1 : 5, 1 : 10 and 1 : 20, but not in dilution 1 : 50 even the next day. The tubes containing Serum A and Serum B showed a slight clot in the dilutions of 1 : 5 in two hours, but no clot in the other dilutions. This shows conclusively that Serum D is poorest in thrombin but much richer in serozyme.

Experiments with fresh serum from ordinary normal blood clotting spontaneously show some thrombin activity, practically none the next day. Such a serum used the next day as serozyme is very weak and somewhat variable. One assumes that the elements furnishing the serozyme are in sufficient abundance to join with nearly all of the elements which we call cytozyme to form thrombin and leaves behind very little unused serozyme.

QUANTITATIVE ACTION OF THROMBIN

Thrombin is not a ferment, and is able to coagulate only a definite amount of fibrinogen. The following experiment bears on this point:

Experiment 29.—Take four tubes, A, B, C and D; each tube contains 0.4 c.c. of the recalcifying fluid, 0.1 c.c. of serum and 1 drop of the suspension of platelets; after 15 minutes we have the formation of thrombin and proceed to test it in various ways. To Tube A add 0.5 c.c. of the diluted dioxalated plasma; this is the classical experiment and coagulation takes place in less than three minutes. To Tube B we add 0.5 c.c. of plasma which has been dioxalated but not diluted. In this case we have the same amount of oxalate but considerably more fibrinogen. Coagulation takes place in eight minutes. Tubes C and D have their calcium precipitated by the addition of 0.1 c.c. of sodium oxalate, 0.5 per cent. Five minutes later add to C 0.5 c.c. of diluted monoxalated plasma and coagulation takes place in eight minutes. To Tube D add 0.5 c.c. of non-diluted plasma, oxalated 1 : 1,000. In this case there was no coagulation. In C and D by separate oxalation the activity of the thrombin was somewhat handicapped and while in C it can coagulate a diluted solution of fibrinogen, this small amount of thrombin in D is incapable of coagulating a strong solution of fibrinogen.

We must, therefore, conclude that thrombin is a definite substance which acts quantitatively and not as a ferment.

TIME REQUIRED FOR THE FORMATION OF THROMBIN

Thrombin is not formed at once by bringing in contact the two active principles cytozyme and serozyme in a favorable calcium medium. The following experiment is illustrative of this point:

Experiment 30.—Take 10 tubes and prepare in each thrombin in the usual way by the mixture of 0.4 c.c. of the recalcifying fluid, 0.1 c.c. of serum and 1 drop of the suspension of platelets. At minute intervals add 0.5 c.c. of diluted dioxalated plasma. There will be no real coagulation in the tubes in which the contact has been under seven minutes; where the contact has been seven minutes or longer there is firm coagulation inside of two minutes after the fibrinogen is added.

Using both the diluted dioxalated plasma and also the method of separate oxalation, the time was fairly constant at about seven minutes in many experiments. It is of considerable interest that Bordet and

Delange, working with rabbits, found that the necessary time of contact was only one and five-tenths minutes. This is one of the variations between human and rabbit blood. Another constant and interesting result of these experiments was that the coagulation was apparently just as rapid and just as firm when the contact was seven minutes as when it was prolonged to twenty or twenty-five minutes. This suggests that the formation of thrombin is delayed for a definite amount of time, but that once begun the formation occurs almost instantaneously. Against this argument is the fact that oxalated plasma which contains many platelets, coagulates in a few minutes (six to ten) on recalcification, while a very clear plasma containing very few platelets requires thirty minutes or sometimes even forty-five minutes, for coagulation on recalcification. It is true that a very weak thrombin requires a considerable length of time for the change of fibrinogen to fibrin, and this may be the explanation of the delay in the case of a recalcified oxalated plasma, poor in platelets. In the ordinary experiments the conversion of fibrinogen into fibrin by a reasonable amount of thrombin takes place rapidly (under two minutes). The time-consuming element in the whole process of coagulation seems to be in the formation of thrombin. The length of time of contact *in vitro* between the various elements necessary for the production of thrombin is about seven minutes in our experimental production of thrombin. This corresponds very closely to the coagulation-time of blood taken from the vein and allowed to clot spontaneously as in the method used by Lee and White,[15] who found the normal coagulation-time to average six and one-half minutes.

It has long been known that temperature has a very marked effect on the time of coagulation. The temperature variation in coagulation-time probably concerns the reaction whence thrombin results.

SUMMARY OF OUR WORK ON THROMBIN

1. Active thrombin formation can be prevented by the presence of concentrated sodium chlorid solution, by sodium citrate, by the absence of calcium and by the presence of barium, which absorbs the serozyme. Once thrombin is formed, however, none of these substances will prevent its action on a fibrinogen solution.

2. It is true, however, that a weak thrombin does not act as well in a medium from which the calcium is precipitated out before the contact with the fibrinogen solution is made. This is shown in the differences between the action of thrombin in the method of separate oxalation and when put in contact with the dioxalated plasma.

3. It has also been shown that thrombin requires a definite amount of time for its formation. This amount of time is considerably longer in human beings than in rabbits.

4. The amount of thrombin is shown to depend on the amount of serozyme and cytozyme used.

5. Thrombin once formed deteriorates rapidly and can barely be demonstrated in the media used in our experiments after twenty-four hours.

6. Thrombin is not a ferment and can coagulate only a certain amount of fibrinogen solution.

7. It has been shown under cytozyme that thrombin can be formed when cytozyme from any of the various sources unites with the serozyme of the blood.

GENERAL SUMMARY

We have been able to demonstrate that the fundamental principles in coagulation as studied by Bordet and Delange in rabbits' blood also hold true for normal human blood.

The differences which we have found are minor ones. We have found that thrombin requires a longer time for its formation in human blood than in rabbits' blood. We have also found that the minimum amount of serozyme required to permit coagulation to ensue is larger in human blood than in rabbits' blood.

We have been unable to confirm the work of Bordet and Delange on the use of peptone as cytozyme. This is probably due to differences in the preparation of peptone.

Although our argument is open to possible objections, we have shown that white corpuscles can be used as cytozyme; they are perhaps not as efficacious as blood-platelets or tissue juice.

We have not been able to employ as cytozome the heated muscle juice of non-human animals in our work on human blood. This is somewhat different from the findings of Bordet and Delange, and tends to confirm their suggestion that there is a certain amount of specificity in the action of the various elements of coagulation.

We have been able to pursue somewhat further than they the investigation of the active principle serozyme and have apparently found it intimately associated with the globulins of the blood.

We have described a modified technic of obtaining human blood which has given very satisfactory oxalated plasma.

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ULCUS VENTRICULI *

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PATHOGENESIS

Notwithstanding that a great deal of experimental work has been done to explain the pathogenesis of gastric ulcer, the real etiology is as yet not clear. We, therefore, consider it a duty to analyze the work and theories advanced, and if possible draw conclusions which will somewhat elucidate the subject.

The fact that ulcus rotundum only occurs in the stomach and its immediate vicinity has given rise to the theory that the gastric juice had something to do with the formation of the ulcer, hence the name "ulcus pepticum."

The question soon arose: What is it that really protects the gastric mucosa against autodigestion? Various authors have tried to answer that question by different explanations.

Hunter saw the protective agent of the gastric mucosa against autodigestion in the principle of "life"—i. e., that living tissue cannot be digested.

Claude Bernard[1] contradicted Hunter by experimental proof, inasmuch as he showed that the leg of a living frog is digested in gastric juice.

Pavy[2] attributed the protection of the gastric mucosa against autodigestion to the alkaline blood circulating through the stomach walls.

Stricker[3] saw in the mucus of the stomach a protective agent against the autodigestion of the stomach.

What are the disturbing factors that allow the gastric juice to digest certain portions of the stomach, causing ulcer?

Virchow[4] saw disease of the blood-vessels as a factor, inasmuch as an ischemia is produced, thereby causing disturbance of nutrition and leading to autodigestion.

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* Submitted for publication Sept. 4, 1913.

[1] Bernard, Claude: Leçons de physiologie experimentale, Paris, 1856.

[2] Pavy: On Gastric Erosions: Guy's Hospital Reports, 1868, xiv, 464.

[3] Stricker: Ueber den Einfluss der Magensaft-Absonderung auf den Chlorgehalt des Harnes, Berlin klin. Wchnschr., 1887, p. 768.

[4] Virchow: Historisches Kritisches und Positives zur Lehre der Unterleibs affectionen, Virchow's Arch. f. path. Anat., v, 364.

While O. Cohnheim[5] conceded that there is a local circulatory disturbance, he could not agree that the disease would be primarily in the blood-vessels, because were that the case ulcer would be a more frequent disease in arteriosclerotics; we find, on the other hand, that ulcer is a disease of the young.

Another argument against the theory of local blood-vessel disease is the fact that we so rarely meet with syphilitic ulcers of the stomach, although we know that syphilitics are so frequently subject to endarteritis; the same is also true of those afflicted with tabes dorsalis, who, as we find, frequently have hemorrhages from the stomach without any local ulcers.

The results of animal experimentation in producing secondary injuries and consequently autodigestion of the stomach, are the following:

Schiff[6] intersected the talami and cerebral peduncles, producing hemorrhagic infiltration in the stomach, erosions and even ulcer formation. He explained his results as neuroparalytic hyperemia, caused by injuries to the central vasomotor nerve trunk of the stomach.

O. Cohnheim injected suspension of plumbic chromate into the stomach circulation, by which he succeeded in blocking only the branches of the mucosa and submucosa; at the autopsy he discovered large ulcers with abruptly descending edges and clean bases.

Koch and Ewald[7] caused gastric ulcer by section of the spinal cord, and after that introducing strong hydrochloric acid into the stomach, so causing deep penetrating ulcer.

Ritter[8] and Decker[9] produced ulcer by trauma and thermic irritation. Silberman[10] caused ulcer by producing hemoglobinuria.

The last two explain to us the clinical relation of ulcer in some cases in which hot food is quickly swallowed (cooks), and the ulcer in malaria which is so frequently associated with hemoglobinuria.

Quincke[11] produced ulcer in animals by bleeding them to a severe anemia. (Our clinical deduction of the frequency of ulcer with chlorosis.)

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[5] Cohnheim, O.: Zur Frage der Selbstverdauung des Magens, Vorlesungen ueber allg., Pathol., 1880, ii, 50.

[6] Schiff: Ueber die Gefaessnerven des Magens, Arch. f. Physiol. Heilk., 1854, xiii, 30.

[7] Koch and Ewald: Arch. f. exper. Pathol., vol. ii.

[8] Ritter: Ueber den Einfluss von Traumen auf die Entstehung des Magengeschwürs, Ztschr. f. Klin. Medizin., xii, 592.

[9] Decker: Experimenteller Beitrag zur Etiologie der Magengeschwürs, Berl. Klin. Wchnschr., 1887, p. 368.

[10] Silberman: Experimentelles und Klinisches zur Lehre vom Ulcus Ventriculi rotundum, Deutsch. med. Wchnsch., 1886, No. 29, p. 499.

[11] Quincke: Die Entstehung des Magengeschwürs, Deutsch. med. Wchnschr., 1882, No. 6, p. 79.

The effect of circulatory disturbance on the development of ulcers of the stomach has also been studied through animal experimentation.

Pannum[12] caused hemorrhagic infarcts and ulcers of the gastric mucosa by injecting an emulsion of wax particles into the central portion of the femoral artery in dogs.

O. Cohnheim[13] produced ulcers in dogs analogous to ulcers in men by injecting a suspension of chromate of lead into the splenic or gastric interior.

Talma[14] caused ulcer by producing anemia in the stomach as a result of faradic irritation.

While the vascular experiments are proof as to ulcer formation in animals, we clinically do not frequently find ulcer of the stomach as a result of emboli or thrombi.

According to D. Gerhard,[15] small ulcers resembling hemorrhagic erosions may be caused by the swelling of ruptured follicles.

Undoubtedly, many superficial ulcerations occur which do not develop into typical ulcers; to this category belong the hemorrhagic erosions of Rokitansky.

That erosions lead to ulcer only in a minority of cases can be proven by the fact that in the circumscribed hemorrhagic areas in the gastric catarrh of alcoholics, in acrobats who introduce sharp bodies into their stomachs, follicular swellings are often found, but no ulcerations.

We see, therefore, that a factor outside of the stomach, either of constitutional origin, like status asthenicus, chlorosis, vagotonia (Eppinger and Hess[16]), or other chronic diseases that would influence the general nutrition, must be causative in the pathogenesis of ulcus ventriculi. This leads us now to the newer and latest work done to establish the above contentions. Before proceeding, however, we must mention the fact that Boetcher and Latulae[17] attribute the causation of ulcer to bacterial invasion. They demonstrated bacteria in colonies on the floor of the ulcer.

Türk[18] produced ulcer by injecting colon bacilli.

Recently the association of ulcus ventriculi with rheumatism, rheumatic endocarditis and tonsillitis has been noted.

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12. Pannum: Experimentelle Beitrage zur Lehre von der Embolie, Virchow's Arch. f. path. Anat., 1862, xxv, 308.

13. Cohnheim: Pathologie der Verdauung: Vorlesungen ueber allg. Pathol., ii, 22.

14. Talma: Cited from Riegel's "Diseases of the Stomach," 1903, p. 554.

15. Gerhard, D.: Zur Diagnostik und Therapie des runden Magengeschwürs, Deutsch. med. Wchnschr., 1888, p. 74.

16. Eppinger and Hess: Zur Pathologie des vegetativen Nervensystems, Ztschr. f. klin. Med., lxvii, 205, and lxviii, 345.

17. Boetcher and Latulae: Diseases of the Stomach, Hemmeter, 1903.

18. Türk: Experimental Gastric Ulcer, Jour. Am. Med. Assn., 1906, xlvi, 1759.

Stockton[19] introduced a neurotrophic theory:

Agreeing that gastric ulcer occurs on a devitalized gastric mucosa being acted on by gastric juice, what is it that, at such an early age, leads to a devitalized condition, causes ulcer and prevents healing? In his masterful paper he explained the ulcer as a result of a local neurotrophic condition analogous to herpes, indiopathic hematoma, and Raynaud's disease.

The neurotrophic theory excited attention, and R. Dala-Vedora[20] experimented on forty-three animals, excising the vagus and injecting alcohol into the vagus, the celiac plexus and splanchnicus.

In all experiments on the vagus results were negative, while injury of the celiac plexus caused erosions and even necrosis of the gastric mucosa.

Von Yzeran[21] succeeded in producing gastric ulcers in rabbits by cutting the vagus below the diaphragm.

Gunderman[22] attributes the occurrence of ulcus ventriculi to what he calls a disfunction of the liver (disturbed function of the liver), based on the experiments of Friedrich and Engelhard, who produced ulcus by ligating the mesenteric vessels, and those of Payr, who produced ulcus of the stomach by injecting caustic liquids into the vessels of the stomach.

The same authors also found changes of the liver, besides the ulcer of the stomach. Based on that, Gunderman in a number of rabbits ligated the main left branch of the portal vein and found that besides the local atrophy of the liver, there resulted an acute ulcus of the stomach, and in one animal that survived forty-eight days the ulcus adapted all the characteristics of a chronic ulcus pepticum. In some instances even a duodenal ulcer was produced, and in one dog he succeeded in producing an ulcus ventriculi by the same experiment. He concluded from that that normally there are formed toxic substances which, however, by the normally functionating liver cell are rendered non-poisonous. If the liver cells are diseased, this disintoxication cannot be accomplished.

The fact that through injection of liver extract one can produce ulcus ventriculi, or intestinal bleeding, is, according to Gunderman, a proof of the toxic influence of the dead liver cell.

On further investigation the question naturally arises, why do such ulcers only occur in certain parts of the stomach, and why do they heal with such great difficulty?

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[19] Stockton: Etiology of Gastric Ulcer, Med. News, Jan. 14, 1893, p. 34.

[20] Dala-Vedora: Experimenteller Beitrag zur Kenntniss der Pathogenesis des Ulcus Ventriculi, Arch. f. Verdauungskr., viii, No. 3, pp. 255 and 411.

[21] Von Yzeran: Experimentelles zum Magengeschwür, Ztschr. f. klin. Med., 1901, lx, No. 3, p. 81.

[22] Gunderman: Versaml. der Deutsch., Gesellsch. f. Chirurg., Berlin, March 26-9, 1913.

Schuetze[23] bases his theory on the fact that ulcer of the stomach can only result at a point where the mucosa is not properly protected (locus minoris resistentiae). He utilizes as a foundation for his theory the findings of Adolf Schmidt, Lange, Faber and others, who found in certain portions of the stomach an epithelium resembling intestinal epithelium, and that many such cases had achylia during life. Schuetze argues that in cases in which acid is present, the above named epithelium is destroyed, the mucosa not protected, resulting in ulcer. This would also explain why ulcus is more common in the young, because the epithelium is of embryonic origin.

Ashhoff[24] points out that the seat of the ulcer is mostly situated in one of four parts of the stomach. These parts (he speaks of *"Engen,"* i. e., narrowings) are brought about by surrounding organs; near the cardia by diaphragmatic pressure at the antrum cardiacum; lesser curvature, by pressure by the aorta; at the pylorus by the spine; and at the duodenum by the head of the pancreas.

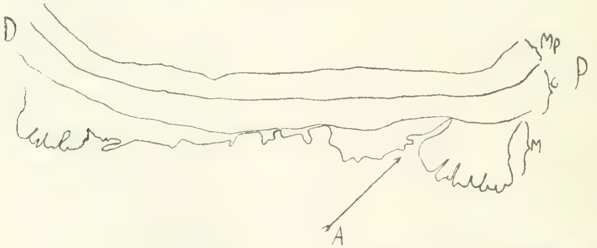

Fig. 1.—Ulcus ventriculi (Aschhof); P, proximal part of the ulcer; D, distal part of the ulcer; M. mucosa; C, connective tissue; Mp, muscularis propria; A, undermined brim of the proximal part and direction of progress of the ulcer.

The flow of the chyme forcing itself through these narrower areas mechanically (according to Aschoff) brings about ulcer formation.

By the same mechanical theory he explains the progress and the characteristic form of ulcer. The chyme passing the ulcerated area has a tendency by its mere force to irritate the proximal brim of the ulcer producing proliferation and thickening, and grinding off the distal part, causing it to appear lower than the proximal part.

The passage of the chyme wave is also held responsible by Aschhoff for undermining the thickened proximal brim and so causing the progress of the ulcer in that direction (Fig. 1).

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[23] Schuetze: Wien. klin. Wchnschr., No. 11, 1912.

[24] Aschoff: Lectures, Mount Sinai Hospital, New York, 1913.

We personally are inclined not to accept the theory of Aschhoff that narrowing is responsible for the seat of the ulcer at the points outlined by him.

Firstly, ulcers may be found in almost any portion of the lesser curvature, sometimes more anteriorly, and sometimes more posteriorly.

Secondly, the position of the stomach varies in different individuals (ptosis, vertical position, etc.).

Thirdly, because of the adaptibility of the stomach to pressure influence.

Aschhoff's explanation of the form and progress of the ulcer is more convincing.

Eppinger and Hess, in their brilliant experimental work on the vegetative nervous system (vagus, sympatheticus), show the importance of the influence of the vagus and sympatheticus on the functions of the different organs, and they point out that where the vagus tone of the gastric mucosa is in a state of hyperirritation, that hypersecretion and hyperacidity, as well as spastic contractions of the gastric muscle, lead to ischemia and ulcer formation.

Continuous spasticity prevents the healing of such ulcers. According to Eppinger and Hess, therefore, ulcer of the stomach occurs in individuals with stigmata of vagotonia.

Roessle[25] calls the ulcus ventriculi a "second disease," second to a disease outside of the stomach (appendicitis chronica; cholelithiasis; chronic obstipation), which by way of the visceral nerves causes contractions of the musculature of the stomach, thus leading to ischemia and ulcer formation.

Lichtenbelt[26] through his numerous experiments advances the explanation that ulcus is the outcome of spastic contractions of the muscularis mucosa, not the muscularis propria, thereby constricting the blood-vessels and causing ischemia and ulcer. As an underlying factor he considers the neuropathic predisposing element essential.

Eppinger and Hess, Roessle, and Lichtenbelt, have stimulated von Bergman[27] to advance the theory of the so-called "spasmogenic ulcus pepticum."

Von Bergman holds that, on account of spastic contractions of the muscularis mucosa, the local blood-vessels become obstructed and the mucosa digested.

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[25] Roessle: Das Magengeschwür eine zweite Krankheit, Mittheil. Grenzgeb., xxv, 4.

[26] Lichtenbelt: Ulcus Ventriculi, Gustav Fischer, 1912.

[27] Von Bergman: Das spasmogene Magengeschwür, München. med. Wchnschr., 1913, No. 4, p. 169.

According to Boeninger and others (*Verein f. innere Medicin,* March, 1913) spastic contractions lead not only to ischemia, but also to hemorrhages of small blood-vessels.

The prevention of healing and further tendency to chronicity is due, according to von Bergman, to continuous spastic contractions of the muscularis. These contractions are the result of an underlying neuropathic tendency, and he cites fifty-eight out of sixty patients with ulcers who showed neuropathic stigmata of the vagosympaticus type.

To show how much attention has of late been paid to the general status as a predisposing factor to ulcus ventriculi, we cite the theory of E. Stoerk,[28] who considers the status lymphaticus an important factor in the etiology of ulcus ventriculi. Those affected with general lymphatismus, Stoerk says, likewise have an increase in the lymphatic element in the stomach; their follicles are more readily irritated and respond with an état mameloné (a marked increase in follicles) which serves as a mechanical hindrance. Besides that he also states that those that are of the status lymphaticus have likewise disturbances of the vegetative nervous system, and that they are predisposed to bacterial infection, hence the difficulty of the healing of the ulcer.

In spite of all the theories and experimental work enumerated thus far, coming from such conscientious and painstaking observers, and really throwing so much light on the subject, from a clinical aspect one does not feel that all the requirements are covered in explaining the pathogenesis of ulcus ventriculi.

We shall attempt, therefore, to analyze the origin of ulcer as the result of a mechanical disturbance of the stomach. In order to develop our views, we shall have to dwell somewhat on that part of the anatomy of the stomach most concerned with the mechanical power of the stomach, i. e., the musculature.

The musculature of the stomach consists of the muscularis of the stomach wall proper—muscularis propria—and the muscularis of the mucous membrane—muscularis mucosa.

The muscularis propria consists of two layers—an outer layer, formed by the longitudinal fibers, and an inner layer, formed by the circular fibers. The longitudinal fibers coming down from the esophagus, run along the small curvature in a more compact manner to the pylorus, while these fibers on the lateral wall of the stomach, as well as on the fundus, are distributed relatively thinly and apart from each other. On the greater curvature and at the pars pylorica the longitudinal fibers are again somewhat more defined where they appear in more continuous and compact manner; part of them go to the first part of the duodenum, most of them terminate in the sphinctor pylori.

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[28] Stoerk, E.: "Ulcus und Lymphatismus," Deutsch. med. Wchnschr., 1913, No. 11, p. 496.

The circular fibers of the esophagus appear in stronger bundles in the region of the cardia, and in thick distribution at the small curvature, spreading out more thinly to the fundus and the rest of the stomach, until they reach the pylorus, where they form a strong ring—the sphinctor pylorii.

The so-called fibrae obliquae which all anatomists at first considered a part of the innermost circular fibers, running obliquely from cardia to fundus, and spreading toward the fundus, are considered by the Swedish anatomist, A. Retzius,[29] not as a part of the circular fibers, but as a separate third and innermost layer of muscle fibers, characteristic of the stomach only, and not found in any other part of the gastro-intestinal tract.

The fibrae obliquae lie like a muscular belt around the left side of the cardia (see Fig. 2) from where they spread to the front and back wall of the stomach, continuing to the antrum pylori.

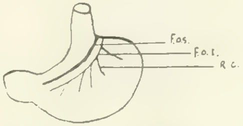

Fig. 2.—Schematic drawing of the stomach; F. o. s., fibrae obliquae, pars superior; F. o. i., fibrae obliquae, pars inferior; R. c., rami communicantes.

They ride, as it were, on the cardia and continue to a small part of the esophagus.

To explain the physiological function of the fibrae obliquae, we must accept with Willis an upper, more horizontal part of the fibrae obliquae, strongest at the cardia and in the region of the lesser curvature, and a more oblique part, which runs along the lateral wall of the stomach, ending at and dipping into the pylorus ring, and communicating by short branches with the circular fibers of the muscularis propria of the stomach. The function of the fibrae obliquae, according to R. Kauffman,[30] who calls it "horse-shoe loop" (Fig. 3) is to bring the upper part of the anterior and posterior wall of the stomach in the region of the lesser curvature nearer to each other. According to A. Retzius the upper horizontal part of the fibrae obliquae forms by its contraction a groove

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[29] Retzius, A.: Bemerkungen ueber das antrum pylori beim Menschen und einigen Thieren, Arch. f. Anat. Physiolog., 1857, p. 74.

[30] Kauffman, R.: Anatomisch experimentelle Studien ueber die Magenmuskulatur, Ztschr. f. Heilk., 1907, xxviii.

(as in ruminating animals) along the lesser curvative, which, depending on innervation, close at regular intervals and more or less tightly.

The function of the lower bundle of the fibrae obliquae, due to their rami communicantes with the circular fibers of the stomach musculature, and their collaboration, is to cause local contractions of the stomach (*"loculamente"*) identical with and serving the same purpose as the intestinal segmentations (Cannon). These bundles, by their peculiar distribution, form the connecting link between the pars pylorica and the Retzius groove on one hand, and the fundus on the other. In this manner liquid and solid food substances can pass through the groove—with the exclusion of the fundus proper—from the esophagus directly to the pars pylorica, and backward by way of antiperistalsis from the sphinctor pars pylorica toward the esophagus.

This antiperistalsis has been proven by W. Beaumont,[31] Cannon[32] and O. Prym.[33]

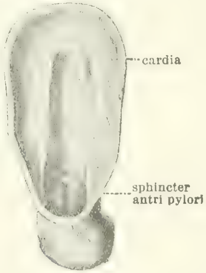

Fig. 3.—"Retzius Groove" (R. Kaufmann, Ztschr. f. Heilk., 1907, xxviii).

We therefore see that the musculature of the stomach is thickest and strongest at the pylorus—3½ mm. Next to that, the lesser curvature and cardia—1½ mm. and more, and thinnest at the fundus—1 mm., and in some parts 0.4 mm.

It is evident from the distribution of the musculature that the stomach can safely be subdivided into two compartments, one corresponding to the fundus (corpus), and the other to the pylorus and lesser curvature (Kauffman[30]). The fundus with its poorly developed musculature may be compared to the auricle, while the pylorus and lesser curvature with its strong musculature, is comparable to the ventricle of the heart.

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[31] Beaumont, W.: Neue Versuche ueber den Magen Saft. Translated by B. Luden, Leipzig, 1834, p. 75.

[32] Cannon, W. B.: The Movements of the Stomach, etc., Amer. Jour. Physiol., 1898, p. 359.

[33] Prym, O.: Die Entleerung des Magens, die Trennung des Festen und Fluessigen, das Verhalten des Fettes, Münch. med. Wchnschr., 1908, No. 2.

In contradistinction to the opinion that the Retzius groove is functionally a part of the fundus, we will try to show that the Retzius groove works partially in conjunction with the pars pylorica.

When we now consider the motor function of the stomach according to the experiments of Cannon, Hoffmeister and Schutz,[34] Moritz,[35] Sick,[36] Gruetzner,[37] we see that the greater part of the work of the stomach is done by that compartment where the musculature is most developed, i. e., pyloric part and small curvature. Rieder, Rosenthal and Kaessle[38] showed kinematographically how the pylorus and lesser curvature work harmoniously more actively than the fundus and interchanging with it. The mode of the motor function of the stomach is as follows: As food passes down the esophagus, reaching the cardia, it is then first driven into the fundus (Figs. 4 and 5) where it is knitted by the peristaltic action of the fundus. The food impregnated with the gastric juice drops down, as it were, into the antrum pylori, which is opened at that stage.

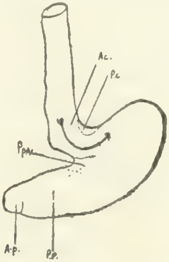

Fig. 4.—Empty stomach (His); Ac, antrum cardicum; Pc, plica cardiaca; Ppa, plica pancreatica; Pp, pars pylorica; Ap, antrum pyloricum. (Nasse and Brecker, Arch. f. Anat., 1905.)

The acid food now excites chemically and mechanically the pars pylorica, causing it to contract, by which contraction part of the food, fit for the duodeum, is allowed to pass through, while coarser particles of the food are, by virtue of antiperistalsis, driven back along the Retzius groove and lesser curvature, to be worked on again and subsequently to be dumped into the fundus (Beaumont).

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[34] Schutz: Ueber die anatomischen Bewegungen des Magens, Arch. f. exper. Pathol., 1886, xx, 1.

[35] Moritz: Studien ueber die motorische Thaetigkeit des Magens, Ztschr. f. Biol., 1896, xxxii, No. 7, p. 313.

[36] Sick: Untersuchung ueber die Saftabsonderung des Magens, Deutsch. Arch. f. Klin. Med., 1906, lxxxviii, 1908; xcii, 169.

[37] Gruetzner: Studien ueber Magen-Bewegung, Arch. f. Physiol., 1905, cvi, 416.

[38] Rieder, Rosenthal and Kaessle: Cong. f. inn. Med., 1909.

The reason we have dwelt somewhat at length on the anatomy of the musculature of the stomach and the motor function is, because it seems to us that there is a direct relation between the strength of the musculature and the location of the ulcer. The mechanical demand made almost exclusively on the antrum pylori and the groove along the lesser curvature explain, in addition to the chemical and thermic irritants, the predisposition of those parts to ulcus ventriculi. The burden laid on the parts just mentioned is doubled if the peristaltic function of the stomach (fundus, corpus) is weakened (atony, dilatation, ptosis).

What is it now, that causes the ulcer formation in these particular regions?

We have learned with certainty that in order to have an ulcer formed, occlusion of the local blood-supply with ischemia (small hemorrhages) and autodigestion is necessary. For the purpose of making our position clear we shall have to review briefly the mode of production of such ischemia, according to the most recent and most plausible views.

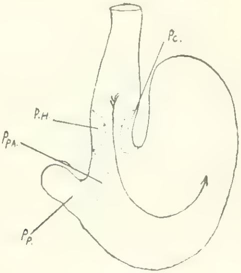

Fig. 5.—Full stomach (His); Pc. plica cardica; Ppa, plica pancreatica; Ph, plica hepatica; Pp. pars pylorica. (Hasse and Brecker l. c.).

Eppinger and Hess see the occlusion of the blood-vessels in the vagosympaticus disturbance, causing spastic contractions of the musculature of the stomach on the blood-vessels, occluding them, causing ischemia.

Roessle also traces the origin of the ulcer to a disease outside of the stomach (appendix, gall-bladder) causing spastic contractions by way of the vagus.

Von Bergman (spasmogenic ulcus ventriculi) is practically in full accord with the views of the three above named authors.

Lichtenbelt demonstrated most conclusively that the contraction of the muscularis mucosa is responsive to irritants with the most violent contractions, occluding blood-vessels and causing ulcerations.

All this shows us conclusively that all previous embolic and stagnation theories have no standing.

We are now to prove how we perceive the origin of the ulcer, based on the views of these authors.

In individuals of the vagus-sympatheticus type, where the vagus symphatheticus disturbance manifests itself chiefly in the stomach, we first encounter a secretory disturbance in the form of increased acidity or increased secretion when symphatheticus elements predominate, diminished secretion when the vagus phenomena predominate always, however, in the form of digestive disturbances. The patient reduces his diet in order to relieve his symptoms, resulting in hypotony; or, he may have a congenital status asthenicus with an inborn hypotony. In the state of hypotony we know, through the studies of Cannon and the Roentgen ray, that the peristole of the stomach is disturbed, or almost abolished.

Excessive work is now thrown on the musculature of the propulsive mechanism of the pylorus and lesser curvature, the food arriving there chemically and mechanically in an unprepared state. For some time the musculature, by an excessive contraction, accommodates itself. Finally comes a time when, in that part (pylorus, lesser curvature) of the musculature most irritated, more than ordinary contractions—really tetanic contractions—take place, contracting on the local blood-vessels, causing ischemia and autodigestion, and leading to ulcer.

What happens if an erosion is once formed? Small, superficial erosions are protected against chemical and mechanical irritation by the spastic contractions of the muscularis mucosa, and heal with minute-scar formation, without giving rise to any marked symptoms during life. But if the erosions are multiple, or the involved area is more extensive from the start, the protection just mentioned will not suffice; spastic contraction will give way to more continuous tetanic contraction, including the muscularis propria, causing more marked symptoms and pain.

These pains serve as a warning, which, if the patient observes a spare diet, may lead to a cure; if, on the other hand, he does not heed the warning, or at the slightest improvement goes back to errors in diet and habits, the continuous irritation prevents healing of the ulcer and aids its progress.

Roessle, as stated, considers ulcer of the stomach a secondary disease to chronic appendicitis, cholelithiasis, etc., and so, by way of the nervous system, causing spastic contraction of the musculature of the stomach, with resulting ischemia and ulcer formation.

While we consider it an established clinical fact, and it has been proven by the Mayos and others conclusively, that ulcus ventriculi is frequently associated with the above-named diseases, we feel, however, that the formation of the ulcer is not by means of the nerves causing the spasms in the musculature of the stomach, but the cause of ulcer formation lies in the stomach itself.

We find that a certain hypersensitive class of people, due to the fact that they have some chronic visceral disease, reduce their diet to a minimum out of fear of pain. From the standpoint of their nervous status the gastric secretion is disturbed, and the same vicious circle occurs here that causes the ulcer on the vagus-symphatheticus basis, viz., peristole almost abolished, on account of the weakness of the fundus muscle, which first gives way to hypotony. The food reaches pylorus chemically and mechanically unprepared, causing greater strain on the pyloric muscle, from where it is thrown back to the Retzius groove along the lesser curvature, where the musculature is most developed, causing abnormal contraction, etc., occluding the blood-vessels, which causes ischemia and autodigestion.

From the fact that some of those suffering with appendicitis, floating kidney, etc., have chiefly gastric disturbances, and that with the removal of the underlying factor the gastric disturbances subside, we can see that functional disturbances of the stomach, secretory and mechanical in type, precede the ulcer formation.

Were the ulcer formed through the nerves causing the spasm of the stomach musculature, as Roessle sees it, we would meet much more frequently than we ordinarily do individuals with ulcer of the stomach.

Given numerous individuals afflicted with the above-named diseases and still never acquiring ulcer of the stomach, how is that to be explained? It seems to us explainable in the following manner: Individuals of the sthenic type, without the stigmata of vagus symphatheticus, have the symptoms of the underlying disease only during the attack, but their condition is not made intolerable by the reflex gastric secretory disturbances which lead to under-nourishment and finally hypotony.

Other direct predisposing factors that play a part in the production of ulcer, like chlorosis, secondary anemia, and malaria, must also have their origin chiefly in the mechanical and secretory disturbances; but here we may have in addition the disease in the vessels themselves (Virchow) predisposing to ulcer.

By far the least frequent ulcers, on the anterior or posterior wall or fundus, have their origin mostly in trauma, either from without (shoemakers; corsets) or from within (cooks; alcoholics).

Sex: It has traditionally come down to us in text-books that females are more prone to ulcer than males. Recently Smithies[39] and Bamberger[40] rightfully pointed out that this is not the case and, corresponding with our experience, that men are even more affected than women.

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[39] Smithies: Gastric Ulcer without Food Retention, Am. Jour. Med. Sc., March, 1913, p. 340.

[40] Bamberger: Ulcus Ventriculi, Hirschfeld, Berlin, 1910.

Age: Ulcers occur mostly between the ages of 15 and 40; with females, in the earlier years and males at later age.

Syphilitic and tuberculous ulcers are caused by the specific virus. In the syphilitics we really find the gummatous, or fibrous tissue formation or ulcer, corresponding to syphilitic affections in other parts of the body.

Up to this point we have endeavored to outline our view of the seat, cause and progress of the ulcer.

What is the cause of the spontaneous healing of ulcus simplex? According to Katzenstein, Blum and Fuld,[41] ulcus ventriculi is the consequence of some circumscribed injury of the stomach wall, which does not heal because the normal proportion of pepsin and antipepsin have been upset, more pepsin being secreted, while there is less antipepsin than normal.

J. Kauffman[42] called our attention to the fact that in hyperacidity and ulcus the mucous secretion in the stomach is increased; he further showed that according to the investigations of Schuetz, Pawlow and Landauer, the mucus has a protective property against the chemical, thermic and mechanical influences on the ulcer. On that the silver nitrate treatment (to be mentioned later) is based, in order to excite mucous secretion when such is necessary. This according to Kauffman, prevents the progress of the ulcer.

Later observers like von Aldor,[43] Schuetz,[44] and the experimental work of Türk,[45] confirm Kauffman's hypothesis that the healing of ulcer depends on increased mucous secretion.

MORBID ANATOMY

The round ulcer macroscopically looks as if stamped out with a die, with characteristic round, sharp outline, of various sizes. The greatest loss of substance is in the mucosa. In old ulcers the muscularis is pulled up to the mucosa. Occasionally the ulcus takes in the whole wall of the stomach, causing marked thickening. This thickening with the seat at the pylorus may simulate a tumor; it is hard and hence its name, callous ulcer. Some ulcers become penetrating, and adherent to neighboring organs. Ulcus penetrating through anterior wall forms a perigastritis. Ulcus penetrating through posterior wall causes adherence of the stomach to pancreas. The same may also be true with ulcer at the lesser curvature with adhesions spreading to the pancreas, as one of our cases proved at operation. Adhesions from the pylorus to the gall-bladder are frequent occurrences.

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[41] Katzenstein, Blum and Fuld: Experimentelles zur Entstehung des Magengeschwürs, Arch. f. klin. Chirurg., Berlin, ci, No. 1, p. 1.

[42] Kauffman, J.: Mangel an Magen-Schleim: Arch. f. Verdauungskr., 1907, p. 616.

[43] Von Aldor: Beitrag.. zur pathologie der Magenschleim Absonderung, Berl. klin. Wchnschr., 1909, Nos. 18-19, pp. 826 and 882.

[44] Schuetz: Berl. klin. Wchnschr., 1909. No. 27. p. 1253.

[45] Türk: Further Observations on the Etiology and Diagnosis of Peptic Ulcer, Brit. Med. Jour., 1907, No. 20. p. 922.

Perforations occur, and these are most frequent when the ulcer is on the anterior wall. If perforation should occur in the region of the pylorus, a localized subdiaphragmatic abscess may form. This abscess may bore its way through into the thorax, forming a pyopneumothorax. Perforation may also occur into any of the neighboring organs.

Microscopically, in a fresh ulcer we see most of the destructive process in the glandular tissue and mucosa. In older ulcers the glandular cells are seen contracted; the cells are sometimes not to be recognized; a few tubules are seen to have undergone cystic degeneration; and a round-cell infiltration is seen in the interstitial tissue of the glands. In still older ulcers connective tissue predominates.

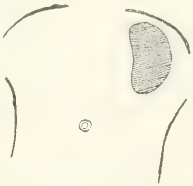

Fig. 6.—Kidney-shaped stomach.

SYMPTOMATOLOGY

Is there such a thing as acute ulcer?

Bolton[46] classes ulcer as acute where the patient suddenly has a severe attack of pain, nausea and hemorrhage; recovering from that he may be free from an attack for the rest of his life, or sometimes another acute seizure may occur. Bolton and others (cited in his article) found post-mortem scar formation where the history had only pointed to one attack. He also counts sudden perforation without previous symptoms to be that of acute perforating ulcers. A case of perforation of gastric ulcer operated by L. Buerger occurred in a man who never had any gastric symptoms before.

Before leaving the subject of what has been described as acute ulcer, we must not lose sight of the fact that acute symptoms and even perforations may occur in chronic ulcers, only the patients who have the ulcer are of the hyposensitive type and hence ignore their symptoms. It is our duty, therefore, even in trivial complaints of the stomach, to follow

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[46] Bolton: Further Observations on Pathology of Gastric Ulcer, Proc. Royal Soc., 1910, lxxxii, 253.

E. Libman's method, viz., to go over the sensory status of the patient very carefully. Like Libman, we had best test the sensibility by pressure on the tip of the mastoid. Very sensitive people cannot stand the slightest pressure; normal people will stand a moderate degree of pressure; in the hyposensitive class even the strongest pressure causes no discomfort.

We repeat that in such people with slight gastric symptoms, we should weigh the history most carefully, and even where one or two symptoms speak for ulcus ventriculi, we should give him the benefit of the doubt, and thus prevent the disastrous acute perforation or milder complications.

PRE-ULCEROUS STAGE

Before we go into the discussion of the symptoms of chronic ulcer, we consider it essential to briefly state some of the symptoms that we clinically class as a pre-ulcerous stage.

By a pre-ulcerous stage we understand a symptom-complex of vague gastric complaints such as a sensation of fullness immediately after meals, belching and sour eructation, various degrees of pyrosis, and, after heavier meals or psychical emotion, real attacks of pain.

We see such symptoms in girls of the age of puberty, in travelers who take their meals irregularly, quick eaters, hearty eaters and those of the status asthenicus type, or those suffering from chronic appendicitis, etc. Such patients are diagnosticated as having ulcus ventriculi by some, others consider them nervous. We feel, as already hinted at in the etiology, that the symptoms are really due to the progressive secretory disturbances, and the spastic contractions giving way to tetanic contractions. Hence we see that in the pre-ulcerated state the pain does not occur at regular intervals after meals, but depends more on the quality, quantity of food and the psychical emotion which in turn influence the secretory and functional conditions of the stomach. In such cases, prophylactic measures, hygienic and dietetic treatment, will completely do away with the symptoms and prevent ulcus formation.

SYMPTOMS OF SIMPLE ULCER

The symptoms depend a great deal on the size of the ulcer. A small-sized ulcer heals completely, with post mortem findings of a scar where, during life, there were absolutely no symptoms, or the symptoms were of such a vague nature that they escaped diagnosis. We explain the course and absence of symptoms in these small ulcers as stated above, by the contraction of the muscularis mucosa on the diseased surface, protecting the affected area from mechanical and chemical irritants. Possibly also the simultaneous mucus secretion neutralizes the acidity and directly protects the ulcerated area.

If, however, a larger area is involved, where the protective agents do not suffice, we get the more pronounced symptoms of ulcus ventriculi. The first symptom that annoys the patient is the pain. To what is this pain due? And has the seat of the ulcus any influence on the time of occurrence of the pain?

We are fully aware that of late a great deal of importance has been attached to the assumption that pylorospasm causes pain. Glaesner and Kreuzfuchs[47] considered the pain entirely due to a reflex from the duodenal juice stimulating the pylorus to contraction, and hence they speak in ulcus ventriculi of two periods of pain, the early and late pain. The former, they explain, occurs just as soon as the food comes into the stomach, as there is a reflex action of the duodenal juice on the pylorus, opening up the pylorus, allowing the food to pass through; the pylorus then closes (chemoreflex, Pawlow) until the food is more alkaline.

In ulcer, according to the above-named authors, although the stomach is at rest during that time, the pylorus is in spasm, and hence the pain. On the same basis they explain the late pain.

Does this correspond to the clinical picture? We must decidedly answer, No!

First of all, in non-complicated ulcer, we never see an immediate pain after meals; just the reverse, the patient is relieved after taking food. Only spicy and irritating food may cause immediate pain by virtue of mechanical and chemical irritation or causing hypersecretion. We explain the pain of a simple ulcer as being due to mechanical and chemical irritation of the ulcerated area, causing spasms in the form of tetanic contractions of the muscularis mucosa and muscularis propria wherever the ulcer is situated.

As to the time of pain, we know through erroneous text-book traditions that the time varies according to the seat of the ulcer; that is to say, if at the cardia, the pain is immediately after meals; if at the lesser curvature, one-half to one hour after meals; if at the pylorus or duodenum, two or three hours after meals.

This, however, does not correspond to clinical observations. We know that the occurrence of pain is in the majority of cases not dependent on the seat of the ulcer. Before we attempt to explain our reasons for the time in which the pain occurs, we will illustrate our findings with two cases.

ILLUSTRATIVE CASES

CASE 1.—A. U., aged 37, laborer; previous history negative, also family history. No status asthenicus. Present complaint dates back to two years before admission to the Har Moriah Hospital, when the patient began to have severe attacks of pain three hours after meals, relieved by taking milk or alkalies. Pain was diffused all over the abdomen, radiating to the back, and sometimes, but not always, relieved on vomiting. Physical examination disclosed pressure-pain in the epigastrium; otherwise negative.

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[47] Kreuzfuchs: Ueber den Pylorospasmus, München. med. Wchnschr., 1913, No. 11, p. 582.

Tube on empty stomach, after a night meal of rice and currants, showed absolutely no food residue either macro- or microscopically, no blood, only an increased gastric secretion — 80 with a free acid of 40.

Ewald's test breakfast, removed one hour afterward, showed well chymified contents two-thirds fluid and one-third solid (hyper-secretion), free acid 60, total acidity 80. No blood in stomach contents, and no occult blood in the stools after frequent examination.

Roentgen ray examination immediately after a bismuth meal showed the stomach in a high state of contraction (hypertonic), with the cardia and pylorus drawn to each other (Fig. 6), the significance of which will be described in the division Roentgen-ray Diagnosis of Ulcus of the Stomach.

Such a form has been observed before by Schmieden and termed "snail" form. When it occurs the ulcer is usually at the lesser curvature. Our case was confirmed at the operation (L. Buerger) as an ulcer of the lesser curvature. According to time of occurrence of pain, the seat of the ulcus would have been thought to be at or even beyond the pylorus.

CASE 2.—A. K., married, belt maker. Negative previous and family history. His history of gastric disturbance dates back ten years. For the last three years he had suffered from severe attacks of pain, three or four hours after meals, relieved on taking food or alkaline powders. He never vomited, but had frequent regurgitation. One year ago he was treated in a hospital where he underwent a regular ulcer cure. After that he was comfortable for a few months, when the attacks became more frequent, always severest three to four hours after meals; in addition he had some annoyance from real pain, more or less constant. He was admitted to our service in the Har Moriah Hospital and the physical examination revealed the following:

Status asthenicus, chest negative, tender over epigastrium, but no direct pressure point. On empty stomach (after a meal of rice and currants the night before) we found 10 c.c. gastric juice, which neither macro- nor microscopically showed any food particles. Ewald's test breakfast removed one hour later showed three-fourths solid, one-quarter liquid. Chemical examination showed free acid 10 and total acidity 25 (sub-acidity). No blood; stools showed on two occasions occult blood, and after that every examination of the stools was negative.

On account of his sub-acidity, the continuous pains, the long duration of the disease and the marked emaciation, a suspicion of malignancy arose, and we utilized the Gluczinsky[48] method. This consists of giving to patients who show an an- or subacidity after Ewald's test breakfast, a Riegel's test meal. If, after this test meal, acid secretion is stimulated to an increase, it speaks for ulcer. In our patient, after the Riegel's test meal, the acidity was markedly increased.

Fluoroscopically an ulcus hour-glass contraction of the stomach was seen, which, according to Haudeck, is indicative of an ulcer of the lesser curvature. Because of the continuous pains and his non-yielding to treatment, adhesions were also considered, and surgical interference advised. At the operation (L. Buerger) an ulcer at the lesser curvature was found, spreading to the posterior wall of the stomach and adherent to the pancreas.

This case, too, well demonstrates the fact that the time of pain would have been a misleading factor in localizing the ulcer. We see, therefore, that the time of occurrence of the pain depends on a number of factors; size of ulcer, quality and quantity of food, and whether one or the other ostium of the stomach is sympathetically involved in aggravating the pain. After a light meal, independent of the seat of the ulcer, the pain occurs one to two hours later; after a heavier meal, three to four hours later. This goes to show that in the early course of digestion, when the stomach is full, the ulcerated part of the stomach is protected by the musculature contracting over it; if the stomach becomes empty, relaxation over the ulcerated area sets in, the eroded surface is then exposed to the food and gastric secretions, and hence the pain. In light meals where such is the case, after one or two hours the pain occurs at that particular period; after heavier meals where it takes three or four hours for the stomach to empty itself, the pain occurs later. In stomachs of marked atony, or gastrectasia, we know from experience that the pain occurs even later than three or four hours, even after five or six hours, and is often relieved after vomiting a little food.

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[48] Gluczinsky: Differential diagnose zwischen Ulcus Ventriculi und Carcinoma ventriculi, Ztschr. f. klin. Chir., 1912.

More information about the localization of the ulcer gives us the direction in which the pain radiates and in what position the patient has most pain. It is a clinical fact that pain radiating more to the right of the umbilicus speaks for ulcer near the pylorus; pain radiating to the left hypochondrium speaks for ulcer on the lesser curvature. With the ulcer at the cardia there are often attacks simulating left intercostal neuralgia.

As to the influence of position on the seat of the ulcer, we often find that a patient with an ulcer in the region of the pylorus is uncomfortable when he lies on the right side, the opposite being true with the ulcer at the cardia.

Pressure-points in localizing the ulcer (the Boas pressure-point between the tenth and twelfth dorsal vertebra to the right, if ulcer is in the pylorus; to the left, if on the lesser curvature; the painful pressure-point in the epigastrium or the painful pressure-point in the epigastric region, especially when the ulcer is on the anterior wall, or a perigastritis, complicates the ulcer) have only a limited value in establishing a diagnosis or localizing an ulcer.

Einhorn's thread with bucket for determining the location of the ulcer consists in letting the patient swallow a bucket attached to a thread and left over night. When withdrawing, we note whether the thread is stained red, and measure the distance from the teeth. This method does not seem plausible for the following reasons: (1) Because not every ulcer necessarily bleeds; (2) even if it does, it is a question whether the thread will even be touched by that part of the stomach where the ulcer is situated.

A very important aid in localizing the ulcer is the x-ray examination, to be described later.

PYROSIS

Pyrosis was always explained as being due to acids — organic or inorganic — in the stomach. returning along the lesser curvature to the cardia, and with simultaneous opening of the cardia the sour fluid entered the mouth (regurgitation).

Clinically, pyrosis is the result of the excessive production of acids in the stomach, introduced into the stomach with the food, or of eating such foods as tend to increase the acids of the stomach, while at the same time the neutralizing agent, viz., the mucus in the stomach, is not produced in proportion to the acid. We can well picture the pyrosis to be the paresthesia of the stomach. Pyrosis does not manifest itself only in the region of the cardia, but with the patient on the right side, the pyrosis is intensified on the right side, and when the patient is on the left side the pyrosis is stronger at the cardia and lower part of the esophagus. Pyrosis is an important symptom in the pre-ulcerous state, and during all stages of ulcer. It is relieved either by taking alkalies or by vomiting, which tends to prove that the excessive acid is mostly responsible for the pyrosis.

ACIDITY

An increase in the free HCl and total acidity have been considered to constitute an important symptom of ulcus ventriculi. It was even thought that excessive hydrochloric acid was essential in bringing about the ulcer. To-day we know that the gastric juice is non-essential to the production of ulcer, and everything being equal, ulcus may be even produced with a gastric juice of a normal acidity or even of subnormal acidity. However, as we have already learned from the etiology that ulcus ventriculi frequently occurs in individuals that have a tendency to hyperacidity, this may explain why in a great majority of cases of ulcus we frequently find hyperacidity.

In Mayo's clinic, Smithies found hyperacidity in the majority of 140 cases operated on for ulcus; he also found that the free HCl was highest when the ulcus was at the pylorus, while the total acidity was highest when the ulcus was at the lesser curvature on the anterior wall.

Clinically, we find many cases which show hyperacidity during some stage of the treatment, later changing to subacidity and rarely even to anacidity. Notwithstanding a low acidity, the patient has the discomfort of hyperacidity.

H. Strauss[49] termed such cases anacida hyperacida, which he attributed to hyperesthesia of the mucous membrane.

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[49] Strauss, H.: Die Dietbehandlung des Magengeschwürs, Jahreskurs. f. aertzl., Fortbild., August, 1911, p. 55.

We believe that the mucous secretion which serves as a protecting agent against the irritative property of the gastric juice is diminished, and hence even a low acidity tends to produce discomfort.

Riegel explains the diminution of acidity, where there was hyperacidity before, as due to the gradual exhaustion of the acid secretion. In cases of ulcus where we find subacidity, we are sometimes inclined to doubt the existence of ulcus, or suspect carcinoma on the basis of ulcer. To determine this, Gluczinsky[48] gives us a very important clue. Where patients have a subacidity with Ewald's test breakfast, he subsequently gives a Riegel's test-meal, and if he finds the acidity increased, he considers it characteristic of ulcer.

HYPERSECRETION

Strauss and Bamberger[50] consider hyperacidity and hypersecretion as depending on the same source. We find clinically that hypersecretion is even more frequent in ulcus ventriculi than hyperacidity. At times hypersecretion may be intermittent; at other times we can only bring about a hypersecretion after the patient partakes of food. Such a form of hypersecretion is correctly termed by Strauss alimentary hypersecretion. The so-called continuous hypersecretion that Reichmann described as an independent disease, is more frequently an expression of ulcus ventriculi, or ulcus duodeni.

A functional continuous hypersecretion is only of a transitory nature. Gluczinsky called attention to the fact that when there is a hypersecretion the sodium chlorid in the urine is diminished or absent.

NAUSEA AND VOMITING

Smithies has found vomiting in ulcus ventriculi more frequent than have other clinicians. In simple ulcer discussed here, vomiting is infrequent and not a constant symptom. If vomiting occurs it usually relieves the pain. The vomiting of simple ulcus is not the result of the ulcus, but it is more characteristic of certain individuals, who with any pain, especially abdominal, are easily subject to nausea and vomiting. A symptom much more frequently met is regurgitation of sour fluid, causing a burning sensation under the sternum and in the throat, and also a sour taste in the mouth.

HEMATEMESIS

Various authors have given the frequency of hematemesis in ulcer as varying between 30 and 60 per cent. Here A. Jacobi's statement is correct, that statistics differ according to whether we deal with hospital material, or ambulatory or private patients. Certain it is that hematemesis is not a frequent symptom. More frequently we find blood coming through the tube. This differs from the blood due to trauma and adherent to the tube, which is bright red and in streaks, while the blood coming through the tube and characteristic of ulcer is fluid, dark red and mixed with gastric juice, sometimes in quantity of 5 to 10 c.c. When we find this we should be cautious with the future use of the tube.

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[50] Strauss and Bamberger: Fortschritte auf dem Gebiete der Magenerkrankungen, Jahreskurs. f. artzl., Fortbild., March, 1913, p. 42.

Hematemesis is characterized by a preceding nausea, marked discomfort in the epigastric region, a feeling of extreme weakness, dimness of vision, and finally hemorrhage. The blood is usually dark, mixed with stomach contents, acid in reaction.

To differentiate the hematemesis between an ulcus ventriculi and carcinoma ventriculi, in the latter the blood mixed with the mucous stomach contents is alkaline, having more the appearance of coffee-grounds and may have a decomposed odor; above all we are guided by the cachexia of the patient, because carcinomatous stomachs bleed, as a rule, profusely in the last stage of the disease, due to the ulceration of the carcinoma. (Microscopical examination may disclose cancer cells and the Boas-Oppler bacillus.)

Hematemesis may occur as a result of cirrhosis of the liver, seldom in the course of decompensated endocardial diseases due to congestion; or to atheromatous changes of the stomach blood-vessels or rupture of small aneurysms of the stomach vessels, as a result of arteriosclerosis, and is differentiated by the history of the case and general findings.

A characteristic case of hematemesis as a result of atheromatous changes of the stomach blood-vessels observed by us is worth citing.

Case 3.—A butcher 57 years of age was admitted to the Har Moriah Hospital in a state of confusion, with a previous history obtained from his family of his suffering a few months before from severe pains behind the sternum. Within a few days the mental symptoms disappeared without leaving signs of any organic nervous disease. He then developed symptoms of intermittent claudication of both lower extremities. With the subsidence of these symptoms abdominal symptoms (angina abdominalis) came to the fore. One year later, with the repetition of the abdominal symptoms, he had severe gastric hemorrhages lasting for a few days. It is now a year and a half since those hemorrhages occurred, and outside of his occasional attacks of angina pectoris he is absolutely free of gastric symptoms.

Other causes of hematemesis not originating in the stomach are: varicosities of the esophagus, small aneurisms of the esophagus, sometimes pulmonary hemorrhages when part of the blood is swallowed, blood coming from the pharynx or nose.

A case of hematemesis as a result of having swallowed blood from an ulcer of the nose was so severe that for four or five days we kept the patient absolutely quiet as a matter of precaution, on suspicion of ulcus ventriculi. Local cauterization of the nose stopped the bleeding and quick recovery followed.

Hematemesis occurs in blood-diseases like pernicious anemia, purpura hemorrhagica and very frequently in "Banti's disease" (splenic anemia).

Vicarious hematemesis replacing menstruation is not infrequent. Cases are cited in which hematemesis repeated itself without any appreciable cause. Charcot drew attention before to this kind of hematemesis. He called it hysteric. We had occasion to observe two such cases in the Har Moriah Hospital — two young girls who had repeated hemorrhages from the stomach, while before and after the hemorrhages they were absolutely free from gastric symptoms. A characteristic feature in both cases was the fact that the hemorrhage was preceded by a state of nervous excitement—flushed face, choking sensation in the throat, no nausea, but marked restlessness.

The cause of hysteric bleeding (Charcot) has never been satisfactorily explained.

Other causes of hematemesis are the bleeding of post-epileptic seizures and injuries to the brain.

In conclusion, we especially call attention to the fact that certain food-stuffs may be vomited that simulate blood; in such cases chemical and microscopic examination will clear up the diagnosis.

OCCULT BLOOD

Another very important symptom to which we should pay careful attention is the repeated finding of occult blood in the stool. We should, however, exclude bleeding from other sources—the gums, pharynx, hemorrhoids, fissures or ulcerations in any other portions of the intestines, and according to Kehr, an ulcerated gall-bladder. The patient should be put on a meat-free diet for at least three days before examination for occult blood. It is certain that occult blood is more frequent in duodenal ulcer than in gastric ulcer.

The repeated finding of occult blood, notwithstanding a perfected ulcer cure, should awaken our suspicion of carcinoma (Elsener). Boas even says that without occult blood no diagnosis of ulcer should be made. With this we differ. We only agree with Boas that where occult blood persists it indicates that the ulcer is in a florid state. It should be mentioned here that as a result of the prolonged oozing a marked secondary anemia may result, sometimes making the patient appear so cachectic that a suspicion of malignancy may arise.

MOTILITY DISTURBANCE

An additional symptom of less frequent occurrence and far less reliable in simple ulcer of the stomach is microscopical stagnation on an empty stomach, after the patient has received rice and currants the night previously. Other authors advise 2 grams of bismuth with the meal of the preceding night, with the idea that the bismuth will stick to the eroded surface and be found the next morning on an empty stomach.

The delay in emptying the stomach is not, according to our opinion, pathognomonic of ulcus ventriculi. If the ulcer is at the pylorus, there is a delay in emptying the food, due to the associated pylorospasm, and individuals who, irrespective of ulcer, have hypo or atonic conditions of the stomach musculature, have delayed motility irrespective of the seat of the ulcer.

We agree with L. Bamberger,[51] who, in a number of cases in H. Strauss' clinic, found occasional microscopical stagnation in absolutely normal stomachs, and there was no microscopical stagnation in ulcers of the stomach. The Roentgen ray examination has taught us that the stagnated food lies in the neighborhood of the ulcer, corresponding to the local contraction.

COMPLICATED ULCERS

If the ulcer progresses, affecting the serosa, the symptoms vary, depending on the seat of the ulcer.

The most serious complication is that of perforation. The onset is acute, with severe pain in the region of the stomach, sometimes described by the patient as a sensation that something tore in the stomach. There is a marked distention of the abdomen, due to the escape of air and stomach contents, obliterating liver and splenic dulness. General peritonitis develops very quickly, usually within ten to twelve hours in the majority of cases.

There is never vomiting, a characteristic point to which Traube first called attention.

It is very seldom that general peritonitis does not follow, and this is the case when perforation takes place on an empty stomach.

Perforation through the front wall may form a localized abscess anteriorly, which is diagnosed by the palpable mass and the septic temperature. Or it may perforate posteriorly, giving rise to a subphrenic abscess (pyopneumothorax subphrenicus, Leyden). There is flatness of the lower part of the chest and the characteristic three zones described by E. Roth: flatness below the diaphragm, an area of tympany above, and above this another area of flatness due to compressed lung tissue.

The septic temperature, the examination of the blood and aspiration will clear up the diagnosis.

Less frequent forms of perforation deserve mention. A case is described by Osler,[52] where the perforation occurred into the left ventricle, and the patient lived for two days. The perforation closed with the systole and opened with the diastole.

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[51] Bamberger, L.: Ueber die diagnostische Bedeutung alimentaerer Restproben bei ungestoerter Magen Motilitaet, Arch. f. Verdauungskr., 1911, xvii No. 3, p. 241.

[52] Osler: Carcinoma of the Stomach, Univ. Med. Magazine, Philadelphia, 1894-5, p. 248.

A case is cited by Fr. Miller,[53] in which perforation occurred into the lung and the patient coughed up particles of food.

Perforation into the colon is sometimes observed, or perforation into the portal vein, causing pyelophlebitis. Carl Wegele observed a case in which perforation had taken place into the urinary bladder. Perforation into the mediastinum with emphysema of the skin may occur. A perforation observed by Murchinson between the stomach and the left hypochondrium, through the ribs, formed a fistula.

ADHESIONS

A very frequent and important complication is the spreading of the ulcer, becoming adherent to other organs. The symptoms of adhesions depend on where the adhesions have taken place. Adhesions around the pylorus may so twist the pylorus as to cause stenosis. Adhesions of pylorus and gall-bladder give rise to stasis in the gall-bladder and jaundice. Adhesions to the pancreas may give rise to disturbances of the pancreatic function.

Above all, our suspicions as to adhesions should be awakened when the symptoms of the ulcer become aggravated, pains are continuous, and the patient does not yield to the ulcus cure. The aid of the Roentgen ray in the diagnosis of adhesions will be discussed later.

ULCUS VENTRICULI CALLOSUM

In old ulcer, as a result of connective tissue formation and small-cell infiltration, a marked thickening results, involving smaller or greater portions of the stomach. Depending on its location, the symptoms differ. A callous ulcer at the lesser curvature may not give any more characteristic symptom than any other chronic ulcer. The diagnosis is based on the Roentgen ray findings, to be described. If such callous formation is at the pylorus, the symptoms of progressive pyloric obstruction with gastrectasia set in.

It would lead us too far to give a special description of pyloric obstruction, but a few characteristic points, due to obstruction caused by a callous ulcer at the pylorus, should be mentioned.

Clinically, such a stenosis is characterized by marked chronicity. Usually we first obtain a history showing the illness to be of comparatively short duration, with absence of marked pain. The chief complaints are frequent vomiting, usually of comparatively small masses, loss of appetite, eructation of sour and offensive odor and marked feeling of distention.

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[53] Miller, Fr.: Ulcus rotundum pepticum, Eulenburg Real. Encycl., Ed. 4, viii, p. 834.

On examination we find the tongue coated; over the abdomen, well below the umbilicus, there is a marked splash, visible peristalsis (stiffening of the stomach, Boas). Introduction of the stomach-tube reveals a marked stagnation.

It takes some time at one sitting, and with the patient in different positions, to wash out the stomach completely. The stagnated food is usually acid; microscopically sarcinae are found.

When we question further into the history the patient confesses to having had pains years before, that make us think of ulcer as a causative factor. On palpation, a tumor is sometimes felt in the region of the pylorus.

An ulcus callosum at the cardia is less frequent and gives rise to symptoms of obstruction at the cardia, with difficulty in deglutition, dilatation of the esophagus above the obstruction, early vomiting of undigested food which is alkaline and mixed with mucus.

A case of callous ulcer is described by F. Sasse,[54] where the callous formation had occupied the greater part of the stomach, and where Roentgenologically there was, in place of the stomach, a narrow shade, and width of the thumb, running from esophagus to pylorus.

A very frequent and important complication is the so-called "hourglass contraction" of the stomach. It is caused by cicatricial tissue formation, localized either near the pylorus or in the median line, or sometimes near the cardia.

The cicatricial tissue divides the stomach into two compartments which communicate with each other by a canal of varying size.

The diagnosis is aided by the history and by inflation of the stomach, which shows the organ divided into two compartments. Another aid in diagnosis is lavage of the stomach by the sudden reappearance of food particles after the lavage water has returned clear before.

A most important and decisive aid in the diagnosis is repeated Roentgen ray examination showing the constriction always at the same place.

ROENTGEN RAY EXAMINATION

In no other pathological condition of the gastro-intestinal tract is it so necessary that the clinical examination precede the Roentgen ray examination as in ulcus ventriculi.

Simple Ulcer of the Stomach.—In 1906, Hemmeter reported cases of simple ulcer diagnosticated skiagraphically by the bismuth sticking to the eroded surface after the entire bismuth meal had left the stomach.

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[54] Sasse, F.: Ulcus ventriculi totale callosum, München. med. Wchnschr., 1913, No. 12, p. 650.

Since then Jonas, Jolasse, Holzknecht, Haudek, Groedel, Faulhaber, von Bergmann, Rieder in Germany, and Pfahler, Cole, Jaches, T. S. Hirsch and Skinner in this country, have contributed greatly to the diagnosis of ulcer by means of the Roentgen ray.

Based on the work of those mentioned and some of our own experience, we will study the ulcer by means of Roentgen ray to determine the kind of ulcer, seat of same and whether complicated.

In simple ulcer, Jonas called attention to the fact that we can locate the seat of an ulcer by pressing the stomach while the patient is being fluoroscoped, and at the point where the patient complains of pain. It is essential that the seat of pain should change on deep inspiration, with the change of the position of the stomach.

A more exact method is the determination of the motility of the stomach, by the time the stomach empties itself. According to Holzknecht, whenever an ulcer is associated with hyperacidity, it matters not whether the ulcer is at the pylorus or a distance from the pylorus, there is a delay in motility by virtue of pylorospasm. Rieder and Faulhaber take exception to that view. They believe, and this coincides with our own experience, that motility disturbance on account of pylorospasm speaks for an ulcer near the pylorus, unless there is an associated atony of the stomach, in which case there would be motility disturbance independent of the seat of the ulcer.

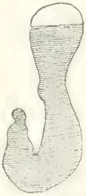

Fig. 7.—Ulcus callosum of small curvature.

Simple ulcer near the cardia gives the picture of cardiospasm. Its rare seat at the greater curvature or posterior wall is so far inaccessible to Roentgen ray diagnosis.

Ulcus Callosum (Chronic small-cell infiltration around the edges of the ulcer).—This form of ulcer is fortunately most commonly situated at the lesser curvature, hence accessible to x-ray diagnosis.

Haudek called attention to the "niche" (nische) symptom characteristic of that form of ulcer. It shews a spot of bismuth on the lesser curvature which empties itself when the stomach is empty. If situated at the pylorus, it interferes with the emptying of the stomach (Fig. 7).

Penetrating ulcers (Fig. 8) are characterized by separate sacks of bismuth with their own air-bag (*Magenblase*) on top.

In the classical article by Holzknecht[55] rules for diagnosis of ulcer are so masterfully laid down that we deem it appropriate to describe them in full.

Based on the fact that whenever there is an ulcus ventriculi there is also a slow emptying of the stomach due to hyperacidity and spasm at the pylorus, and that the sensitive pressure-point is changeable with the position of the stomach either by massaging with the hand while fluoroscoping, or making the patient retract his abdomen while fluoroscoping, the following rule was laid down: Small rest after six hours, sensitive pressure-point changing with the motility of the stomach, no morphological change; conclusion, simple ulcus ventriculi.

Holzknecht and Handell have shown that, where there is antiperistalsis or where the pars pylorica lies to the left, or where there is a snail-form of the small curvature, retraction of the small curvature, transverse stretching of the great curvature, the "niche-form"—all these indicate different stages of ulcus and different complications. Based on the above-mentioned signs, the following rules were laid down by Holzknecht: Small rest after six hours; accompanying sensitive pressure-point; pars pylorica situated high and to the left; snail-form of the lesser curvature; conclusion; old contracted ulcus on the lesser curvature at pars pylorica.

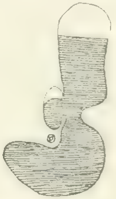

Fig. 8.—Penetrating ulcer.

Another rule: Small rest after six hours; accompanying pressure point at pars media with a sense of resistance; pars media transversely; "niche-form" without air chamber; conclusion, callus ulcer at the lesser curvature, pars media.

HOUR-GLASS CONTRACTION OF THE STOMACH

In hour-glass contraction of the stomach we should differentiate "x-ray" hour-glass contraction (Fig. 9), persistent hour-glass contraction due to fibrous tissue formation dividing the stomach into two distinct sacs (Fig. 10); spastic hour-glass contraction, and depressions on the greater curvature by tumors or gas in the splenic flexure simulating an hour-glass stomach, and carcinoma of the great curvature simulating hour-glass contraction.

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[55] Holzknecht: Roentgenologisches ueber Magen-Erkrankungen, Jahreskurs. f. artzl. Fortbild., August, 1911.

The so-called "x-ray" hour-glass contraction of the stomach is the result of a deep florid ulcer situated at the lesser curvature. The meal passing the ulcerated area causes a contraction of the circular muscle fibers of the stomach, bringing about an indentation of the greater curvature of the stomach.

Watching such a patient take his meal fluoroscopically, we observe the following: The first few spoonfuls slide directly down to the lower sac, at the same time causing the above-described contraction of the curvature so that the rest of the food gathers in the upper sac. This contraction may last from a few seconds to one-half hour; then the stomach relaxes again. This is the reason why such a contraction is not found on the operating table, because under narcosis, and on an empty stomach, there is no contraction.

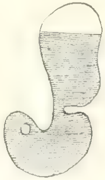

Fig. 9.—Roentgen-ray hour-glass contraction.

Under rare circumstances the longitudinal fibers contract, with the ulcer on the lesser curvature, drawing the pylorus and cardia nearer to each other and the entire stomach upwards and to the left. Schmieden and Haertel have termed such a stomach "tobacco pouch stomach." Holzknecht calls it snail form.

A case observed by us, and confirmed on the operating table (L. Buerger) had the form of a kidney-shaped stomach (Fig. 6). An hour later the contraction relaxed and the stomach adopted its normal shape.

The persistent hour-glass contraction shows skiagraphically two distinct sacs separated by a narrow canal.

Jolasse, Rosenfeld, Jonas and Holzknecht conclusively proved the existence of an hour-glass contraction by first giving the patient bismuth milk, then introducing the stomach-tube and watching the progress of the tube in the stomach. If the tube folds up and deviates to the left, it is considered as characteristic of hour-glass contraction.

In neurotics with spastic tendencies an hour-glass contraction may result, but relaxation occurs after the administration of atropin sulphate, 0.0005 to 0.001 subcutaneously. The hour-glass contraction caused by tumors from without is chiefly characterizel by the displacement of the stomach to the other side, and in order to make a diagnosis we must look at the stomach with the patient in a different position, so that the location of the tumor changes, and thereby exercises no pressure on the stomach.

Perigastritic inflammation may simulate hour-glass contraction.

Franz Groedel cites a case, with demonstration of a photograph, where Rieder's meal distinctly showed two parts — one about the middle of the greater curvature and the second at the antrum pylori. Massaging did not influence the condition. Half an hour later the same stomach was found completely filled and of normal shape. Groedel explains this as follows: The perigastric adhesion does not allow the part of the stomach involved in the adhesion to yield to food as rapidly as the other part of the stomach.

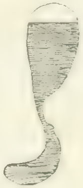

Fig. 10.—Hour-glass contraction of the stomach (anatomical).

Carcinoma at the greater curvature, simulating hour-glass, is differentiated by the ragged appearance of the involved part of the stomach due to a defect of filling.

Haudek also succeeded in differentiating an hour-glass contraction due to ulcer from one due to carcinoma. The former is characterized by a transverse stretching of the stomach, and the constriction is chiefly at the lesser curvature; the latter lies longitudinally, the constriction being mostly on the greater curvature; both walls are usually irregular.

For larger sized tumors of the stomach region the Roentgen ray is only important in determining whether or not the tumor belongs to the stomach proper, which is proven by giving Rieder's meal; if the tumor belongs to the stomach, it will be found that a part of the stomach-shadow is missing.

Pyloric obstruction is characterized skiagraphically by marked peristaltic waves.

Adhesions between stomach and liver show the stomach transversely situated and pulled to the right, with absence of the cap and diminished peristalsis.

DIAGNOSTIC CONCLUSIONS

After our lengthy description of the symptoms of ulcus ventriculi, the question arises: In the majority of cases is a positive diagnosis of ulcus ventriculi possible, and on what do we chiefly base our diagnosis?

Our answer is that it is possible in a great number of cases, but we must always base our diagnosis on a number of factors, and likewise consider the general status of the patient, because, in full accord with von Bergman, patients with status asthenicus are more prone to ulcer.

To enumerate: Pain and hypersecretion, even when existing alone and persistently, are positive proof of ulcus ventriculi. And when these symptoms are present in individuals with status asthenicus and nervous symptoms, so much more reason for the diagnosis of ulcus ventriculi (von Bergman).

Von Bergman is right when he considers the nervous stigmata of the status asthenicus as characteristic of ulcus ventriculi. Our clinical experience teaches us that most of the other nervous symptoms disappear when the ulcer is developed. Hence our conclusions are as follows:

Status asthenicus with nervous symptoms varying in nature, sometimes gastric, at other times cephalgic, or neuralgias of other parts of the body—no ulcer. Status asthenicus with most of the other nervous symptoms subsiding, gastric symptoms, particularly pain and hypersecretion, coming to the fore — ulcus ventriculi has developed.

In hyposensitive people the pain is not a predominating symptom; here continuous hypersecretion alone, or tendency to hyperacidity plus frequent dyspeptic symptoms, is sufficient to establish the diagnosis of ulcus ventriculi. The diagnosis is strengthened when occult blood is repeatedly found, other sources of bleeding excluded. Roentgen-ray diagnosis, as already described, is in some cases a positive clue as to the existence and location of ulcer.

DIFFERENTIAL DIAGNOSIS

The disease from which it is most difficult and sometimes almost impossible to differentiate ulcus ventriculi is ulcus duodeni. We shall, therefore, try first to name the symptoms of ulcus duodeni according to Moynihan,[56] the Mayos,[57] and Bier,[58] and see whether they are characteristic of ulcus duodeni only, or are also found in ulcus ventriculi.

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56. Moynihan: Correlation of Symptoms and Signs in some Abdominal Diseases, Brit. Med. Jour., 1912, Nos. 1, 3, 4, 5, p. 344.

57. Mayo, W. J., and C. H.: Brit. Med. Jour., 1912, No. 17.

58. Bier: Chirurgische Behandlung der Magengeschwürs, Berl. klin. Wchnschr., 1912, p. 368.

Moynihan considers hunger-pain, relieved on taking food, hypersecretion; pain occurring about four hours after a meal, not relieved by vomiting but by taking some food, and the pain more to the right of umbilicus, as characteristic of ulcus duodeni.

Notwithstanding this statement, made by such an authority as Moynihan, we meet clinically with exactly the same symptoms and still the ulcer is even a distance to the left of the pylorus.

In cases in which only the above-named symptoms are present, a differential diagnosis is not possible, and is often made ad operationem, only as outlined by Mayo, i. e., to be guided by the pyloric vein. If the ulcer is to the left of this vein, the disease is in the stomach, if to the right the ulcer belongs to the duodenum.

One point that aids in differentiating is the fact that the symptoms of ulcus duodeni are more prone to appear in certain seasons (winter) of the year. Another characteristic is that even with severe hemorrhages from stomach and bowels as a result of duodenal ulcer, with the subsidence of the symptoms there may be years of freedom, and then a recurrence of the trouble.

Persistent occult blood in the stools speaks, in our opinion, more for duodenal than for gastric ulcer.

Another aid in the diagnosis of gastric ulcer is the Gross duodenal tube. When the tube is in the region of the ulcer, small blood-particles may be seen in the aspirated contents.

Robust individuals have more duodenal ulcer than gastric ulcer. This may explain why duodenal ulcer was considered more prevalent in men than in women.

Of more importance is the painful pressure point, or hammer percussion point (Mendel), which is the point midway between the angle of the ribs and the umbilicus; and Seyferath[59] considers rigidity of the right upper rectus muscle a characteristic symptom.

The occurrence of perforation, not preceded by gastric symptoms, is more frequent in duodenal than in gastric ulcer.

Finally, the Roentgen-ray findings may aid in diagnosis, inasmuch as in duodenal ulcer, notwithstanding the hyperacidity and hypersecretion, there is no motility disturbance, and we have on the contrary, as in achylia, a hypermotility, and invariably see the first portion of the duodenum full.

A differential diagnosis as to whether an ulcer belongs to the duodenum or to the pylorus is so important because the ultimate result is so different. At the pylorus the frequent progress is toward scar formation with symptoms of pyloric stenosis, while in the duodenum, due to the thinness of the wall, if the disease progresses perforation results; hence in the latter, if medical treatment is not quickly successful, surgical intervention ought to be advised.

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[59] Seyferath: Ueber das duodenalgeschwuer, Berl. klin. Wchnschr., 1911, No. 15, p. 852.

To differentiate between a benign and malignant stenosis is essential, when a palpable mass is detected as belonging to the pylorus.

The points which direct us are the following:

Benign	*Malignant*
Marked chronicity with a history of having suffered intermittently for years.	Of more recent date.
Marked gastrectasis.	Slight dilatation; sometimes even a contracted stomach.
Appetite variable.	Almost absent in every case.
Stiffening and peristalsis (Boas) marked.	Very little, or none at all.
Emaciation with anemia.	Cachexia.
The stagnated contents are acid and show sarcinae, or yeast fungi and an acid odor.	Achylia, Boaz-Oppler bacilli and offensive odor.

A very important way of differentiating between benign pyloric stenosis and mere pylorospasm has been pointed out by Holzknecht,[60] by means of the Roentgen-ray examination.

He experimented with papaverin (Merck) and found that in contradistinction to morphin it does not enhance peristalsis and that it hastens emptying of the stomach by about one-third the time. This is accomplished by the property of papaverin to relax circular and longitudinal muscle fibers.

Holzknecht gives patients who show marked stagnation one-fourth to one-half grain of the drug a half hour before the Rieder bismuth meal. In cases in which the stenosis is superinduced by spasm, which is frequently true in benign stenosis, the stomach empties itself much sooner after the administration of papaverin; while in cases of pure pylorospasm the stomach empties itself in due time.

Other diseases that may give rise to difficulties in differential diagnosis we shall only mention, i. e., cholelythiasis, chronic appendicitis, renal colic, chronic pancreatitis and gastric crises.

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[60] Holzknecht and Igollitzer: Papaverin zur Rontgenologischen differential Diagnose zwischen Pylorospasm und pylorus Stenose, München. med. Wchnschr., 1913, No. 36.

The differential diagnostic points between acute hemorrhagic pancreatitis and acute gastric perforation are the following:

Acute Pancreatitis	*Gastric Perforation*
Onset: Sudden.	Usually preceded by gastric symptoms.
Pain: Severest in upper quadrant of abdomen, rigidity localized in the same place.	More diffused; rigidity generalized. Liver and splenic dulness obliterated. A sensation as if something has torn.
Vomiting: Very frequent.	Not frequent, or even absent (Traube.)
Shock: Not marked.	Very marked.
Collapse: More pronounced from the start.	With the development of peritonitis.

ULCUS CARCINOMATOSUM

The development of cancer on the basis of ulcer was at first estimated by Wilson and MacCarty to be about 71 per cent. The studies of Aschhoff and Friedenwald[61] emphatically contradict such frequency. Friedenwald's statistics in 1,000 cases show positively 9 per cent., and 16 per cent. where the relation of ulcer to cancer is of a doubtful nature. Aschhoff's figures are still lower, and according to him, whenever ulcer is found associated with cancer, he considers cancer the primary disease. From a clinical standpoint we are much more inclined to agree with the lower figures.

To diagnosticate the disease where the cancer occurs on the base of the ulcer is of the greatest importance, and every effort should be made to establish an early diagnosis.

Important Points: Persistency of occult blood in the stools and stomach contents, notwithstanding treatment (Elsener); extreme loss of appetite; anemia, gradually adopting the yellowish tinge of cachexia; marked stagnation without a palpable mass. Chemical findings of the acidity getting lower and having no tendency to increase with Riegel's test-meal (Gluczinsky) and, finally, absolute achylia, are positive clues. The Roentgen-ray, showing a defect in filling in certain portions of the stomach, speaks for carcinoma.

PROPHYLAXIS

In prophylaxis we must chiefly consider the class of cases we deal with, and as to what the symptoms present are due.

It is a well-known fact, particularly under American conditions, that many cases of hypersecretion and hyperacidity that gradually led to weakening of the stomach muscles and finally ulcer, are the outcome of over-eating, hasty eating, and without any consideration as to quality. The people should be directed to partake of only two substantial meals daily; one in the morning, consisting of fruit, cereals, eggs, light coffee and bread and butter; only a light lunch at noontime, possibly buttermilk and biscuits; and the second chief meal at 6 o'clock (dinner) consisting of soups, plainly prepared fish and meats, fresh green vegetables, cooked fruits and light puddings. As a rule spicy foodstuffs, canned goods and foods of extreme temperature are to be avoided.

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[61] Aschoff and Friedenwald: On Frequency of Transmission of Ulcer of Stomach into Carcinoma, Boston Med. and Surg. Jour., May 29, 1913, No. 22, p. 796.

A class of persons who, as shown above, incline especially to ulcers is that of the status asthenicus, also having the stigmata of the disturbance in the vegetative nervous system. For these patients diet is of the utmost consideration. We must lay great stress on the essential importance of spare diet (Schonungs-diet) for some time. This consists of meats scraped or minced, vegetables strained, excluding such as have a tendency to gas formation (cabbage, etc.), only fruits which are cooked and strained; bread toasted, soups in the smallest possible quantities, served just as an appetizer; in general, little liquids, especially with meals; the fats of low melting point in sufficient quantities. We believe that in these cases the two-meal system ought also to be adhered to, in order to give the stomach a chance to empty itself. But it is of importance that such patients should rest from a half to one hour after meals, on the right side. Abdominal supports are also essential, and the toning up of the general system by hydrotherapeutics (mild morning douches), sponge baths, or a tempered half bath with cooler water poured over the back and frequent short vacations.

After a while we may start on a coarser diet (Uebungsdiet) or exercise diet, in which the foodstuffs are not so finely prepared.

In the majority of these cases the treatment outlined above will suffice without any medicinal aid.

Some patients, particularly those of the vagotonic type, with their contracted pupils, slow pulse, hypersecretion, moist skin, etc., should be given belladonna in some form.

In a third class of cases, in which the threatened symptoms are due to a chronic appendicitis, gall-bladder diseases, movable kidney or obstinate constipation, the underlying cause must be treated.

TREATMENT OF ULCUS VENTRICULI

Patients with ulcus ventriculi should, as soon as the diagnosis is established, be put to bed, to undergo a regular cure for ulcer.

Of late there has been inclination on the part of some to advocate the ambulatory treatment of ulcus ventriculi, and they claim equal success. We decidedly question whether many of the cases mentioned in literature as being favorably influenced by the ambulatory method actually had ulcers.

Strauss and Bamberger even go so far as to have the patient undergo a regular cure for ulcer when only one or two symptoms, like hyperacidity or hypersecretion, are present. Such a radical course may be practicable under European conditions, where clinics and sanatoria are plentiful, and where there is ample provision even for the workingman to rest as long as necessary without losing his livelihood. In this country however, if repeated examinations show no occult blood, if the patient is fairly well nourished and modification of diet and medicinal treatment, to be outlined below, have a favorable influence, we may for three or four weeks try the ambulatory treatment. But if there be no decided improvement within a week, the patient should be put to bed.

Of what does the ambulatory treatment consist? We must insist on our patient adhering strictly to certain written rules, which are as follows: To restrict his work as much as possible for two or three weeks: to rest after his chief meals for one half to one hour, with warm applications to the epigastrium; to take his meals more frequently, and obey strictly as to quality and quantity, and to avoid all mental excitement and unnecessary bodily fatigue.

Diet: The first week, if there is marked pain, the patient is allowed, until pain subsides, luke-warm milk every three hours; daily quantity between 2½ and 3 liters. For patients who do not tolerate milk alone, we may add either some lime water to the milk, or, mornings and evenings when the patient is at home, add a fine cereal (hominy) to the milk. We can also increase the nutritive value of the milk by adding a half pint of sweet cream to the milk during the twenty-four hours.

Second Week—Morning: One or two soft boiled eggs, cereal, milk soup, one cup of milk. 10 a. m.: one cup of milk with cream, two zwieback and butter. Noon: one or two eggs, cereal, milk soup, one cup of milk. 4 p. m.: one cup of milk, two zwieback and butter. Evening: two eggs, cereal, milk soup, milk with cream, two zwieback and butter. 10 p. m.: one cup of milk.

Third week: Besides the foodstuffs mentioned in the first two weeks, the patient gets 60 gm. of scraped beef or minced veal, or scraped, cooked, unsalted ham, 50 gm. of mashed potatoes, or spinach or carrots in purée form, and toasted white bread.

Fourth week, we add cereal puddings made with butter, milk or cream (non-flavored), and at the end of this week apple sauce or baked apples.

Fifth week, we add to the list of meats, boiled chicken, chopped, sweetbreads or fish, and gradually increase the quantity of meat to 100 grams.

Medicinal, physical and hydrotherapeutic treatment will be discussed below.

TREATMENT OF THE ULCER WITH PATIENT IN BED

Since the time of von Leube, who gave the stomach the most complete rest of five, six and even seven days, in order to arrest peristalsis, diminish acidity and hypersecretion, the treatment of ulcer has changed. Lehnhart even took an extreme view in the other direction, claiming that it is just the starvation that prevents the healing of the ulcer; that because of the hyperacidity and hypersecretion we should supply enough proteins in a non-irritating and easily digestible form to bind the hyperacidity and hypersecretion.

To-day, as we try to base our treatment on the etiology and also to individualize, the treatment cannot be according to either extreme. The argument against von Leube's cure for ulcer, that starvation for the time outlined by him may prevent the healing of ulcer, is certainly not incorrect; on the other hand, Lehnhart's treatment is too radical, because of its tendency to increase stomach peristalsis at a time when rest is so essential for the stomach. The food also irritates the stomach mechanically, and according to Strauss it is liable to cause emboli.

Doubtless at the time when Lehnhart suggested his treatment the differential diagnosis between ulcus ventriculi and ulcus duodeni was not made with such certainty as to-day. The hyperacidity and hypersecretion associated with duodenal ulcer give rise to the so-called hunger pain, because the stomach empties itself quicker; hence in such ulcers, even in the first day of treatment, unless there is acute hemorrhage the Lehnhart course may be indicated.

The treatment that has proven useful to us is as follows: The patient is put to bed, in order to give body and mind complete rest. To give the stomach complete rest, also, no food is allowed by mouth for three or four days, during which rectal feeding is administered.

While the disadvantages of rectal feeding consist of the intestinal irritation that it is liable to produce, and the fact that so little of the food is absorbed that the patient is starved at best, we have on the other hand the advantage of relieving the patient's pain; and with the rectal feeding we introduce fluids into the system which quench the thirst and prevent the drying out of the tissues. These difficulties—the irritation and starvation—can be overcome, the former by adding tincture opii. in the dose of 15 or 20 drops to the nutritive enema, and the latter should be remedied by feeding the patient by the Murphy drop method, to be mentioned below.

METHOD OF RECTAL FEEDING

The first rectal feeding in the morning is preceded by a cleansing solution of normal saline, 1 pint. For some patients more than one cleansing enema a day will have to be given.

Experiments have established the fact that to a certain extent proteins, fats and carbohydrates can be absorbed by the colon, provided the ingredients be given in an absorbable form and be predigested with the corresponding ferments. The absorption of fat, which is the most refractory of these substances, is facilitated by the addition of pancreatin and sodium chlorid. With this object in view Friedman and Strauss[62] have advised the following cream enema:

Cream, 1 pint; pancreatin, 1 teaspoonful; pepton, 2 tablespoonfuls; grape sugar, 2 tablespoonfuls; salt, ½ teaspoonful. (Quantity for one enema.)

The next feeding may be the one advised by Boas:

Milk, one-half pint; 2 yolks of egg; 1 tablespoonful red wine (when there is no hyperchlorhydria); 1 tablespoonful Nestle's or Mellen's food.

Or, instead of this, Riegel's formula:

2-3 eggs; ½ teaspoonful salt; ½ pint peptonized milk.

Or Ewald's, consisting of

3 to 5 eggs; ½ pint 15 per cent. grape-sugar solution.

Outside of the first formula, advised by Friedman and Strauss, which we apply without change, we modify the Boas, Riegel and Ewald's formulae by using:

2 eggs; ½ pint peptonized milk; ½ teaspoonful salt; ½ pint 20 per cent. grape solution, administered slowly.

The grape sugar serves a double purpose, as it adds to the nutritive value by its carbohydrates, and aids markedly in absorption.

Alcohol we do not use in the enemas at all for two reasons, first, because by way of reflex it increases the secretion of the stomach, and second, because it irritates the intestines.

A very useful addition to the caloric value of rectal feeding is the introduction of nourishment per rectum by the Murphy drop method. We use 1 pint of peptonized milk and 1 pint of 20 per cent. grape-sugar solution. Such a feeding is given once a day, the formulas before mentioned twice daily.

If the patient is very thirsty he is allowed to rinse his mouth with cool water, and it is also essential to wash the teeth and mouth a few times daily to prevent parotitis.

On the fourth or fifth day we begin with 2 tablespoonfuls of cooled milk every hour, which amounts to about one-half liter daily. In addition to this the patient is given two rectal feedings—a cream feeding in the morning, and one-half pint of milk and one-half pint of 20 per cent. grape-sugar by the Murphy drop method about 4 p. m.

Just as soon as we find that the patient tolerates well the milk by mouth, we increase the quantity quickly, and on the sixth day we give him as much as 1 liter of milk in divided doses daily, and if his condition permits, we give him two soft boiled or raw eggs daily. If he can tolerate the two eggs and milk, we discontinue rectal feeding, and on the seventh day we increase the milk to 1½ liters daily, and give four eggs daily.

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[62] Friedman and Strauss: Therap. d. Gegenwart, May, 1911.

Eighth day: 1½ liters milk and even 5 eggs; 35 gm. minced veal.

Ninth day: 1½ liters milk with cream; 5 eggs; 1 plate soup; 35 gm. scraped beef; 50 gm. minced veal.

Tenth day: 1½ liters milk and cream; 5 eggs; 1 plate soup: 35 gm. scraped beef; 50 gm. veal; 75 gm. cereal cooked in milk.

Eleventh day: 1 liter milk and cream; 5 eggs; soup; 35 gm. scraped beef; 50 gm. minced veal; 75 gm. cereals.

Twelfth day: 1 liter milk and cream; 3 eggs; soup; 50 gm. scraped beef; 50 gm. minced veal; 3 zwieback; 100 gm. cereal; 100 gm. potatoes mashed

Thirteenth day: 1¼ liters milk and cream; 2 eggs; soup; 50 gm. scraped beef; 50 gm. minced veal; 3 zwieback; 100 gm. potatoes; 100 gm. spinach purée.

Fourteenth day: 1½ liters milk and cream; 2 eggs; 300 cereal soup; 75 gm. beef scraped; 75 gm. veal minced; 5 zwieback; 100 gm. potatoes mashed; 100 gm. spinach purée.

Fifteenth day: 2,000 milk and cream; 4 eggs; soup; 75 gm. scraped beef; 75 gm. minced veal; 6 zwieback; 200 gm. potatoes purée; 100 gm. spinach purée; 50 gm. butter.

In the third week we gradually add toast, well prepared and strained cereals, a squab or fish, lamb chops, calves' brains or sweet breads. By the fourth week we include apple compote, baked apple and strained prunes.

The patient is allowed to leave his bed in the beginning of the third week for a short time during the day, and at the beginning of the fourth week he can remain up all day. While in bed a sponge bath twice daily, and light massage for the extremities ought to be given; also the application of hot flaxseed poultices twice daily for one or two hours, and a Priessnitz at night. The bowels should be kept open by enemas, preferably oil enemata to be retained over night.

MEDICINAL TREATMENT

One of the oldest remedies in the treatment of ulcus ventriculi is silver nitrate. J. Kauffman (New York) showed that silver nitrate exercises its benefit by increasing the mucus in the stomach, thereby protecting the stomach wall and neutralizing the secretion. This is an ingenious idea and has put the silver-nitrate treatment on a rational basis. It is prescribed in the following manner:

Argentinitratis, 0.2-0.3.
Aquae, 120.0.
Ft. solution, 1 tablespoonful.
Three times daily before meals in water.

We must remember, however, that silver nitrate does not agree with some people, because of its irritating property and the fact that it is liable to produce diarrhea and even argyria. It is, therefore, a two-edged sword, and not to be recommended unless other drugs have failed.

Another drug recommended is atropin. Atropin is used for its property of diminishing secretion, and thereby reducing the acidity; most important, however, is its antispasmodic property.

As outlined by von Bergman, atropin is particularly indicated in those patients who, in addition to the ulcer, show stigmata of vagotonia. With this we can wholly agree.

Atropin quite frequently relieves the pain, so that no other narcotics are needed. It is given either internally—0.0005-0.001, or subcutaneously in the same doses, or as belladonna extract 0.03 by suppository twice daily.

A drug more universally used than the above mentioned is bismuth subnitrate. This is an antacid, and also tends to cover the ulcerated mucosa, so serving as a protector. Bismuth is best given combined with magnesium oxid, in order to overcome the constipating effect.

Bismuth can be given in suspension with olive oil; it has then a more decided antacid and soothing effect.

Bismuthi subnitratis	20.0
Magnesia oxidi	10.0
Acquae	200.0

One tablespoonful three times daily one-half hour before meals in one-half tumbler of water.

A remedy which we consider of great usefulness in the treatment of ulcus ventriculi is olive oil, if the patient tolerates it. It is soothing, nourishing and also indirectly antacid, by the reflex action on the duodenum causing a flow of alkaline juice into the stomach; it has also an influence on the intestinal peristalsis. It should be given in ½ to 2 tablespoonfuls, three times a day, before meals.

P. Cohnheim administers oil with the yolk of an egg and 3 ounces of almond infusion. This infusion is made by putting forty sweet almonds and two bitter almonds into boiling water for a few minutes, removing the skins, then grinding the almonds in an almond grinder. Add one half pint of warm water, stirring constantly. Allow this mixture to stand for two hours, then strain through a cloth. It should be freshly prepared each day. If oil is not tolerated at all, sweet cream may be given instead, warm.

The alkaline treatment of L. Bourget[63] has proved very useful. Bourget reasoned that solution of bicarbonate of soda, when given on a full stomach, passes through the fold of Retzius directly to the pylorus, into the duodenum, from whence it regulates the opening of the pylorus, overcoming the spasm and causing a more rapid emptying of the stomach.

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[63] Bourget, L.: Krankheiten d. Magens., Wiesbaden, 1906.

This property of bicarbonate of soda solution indicates that the antacid effect of the drug does not lie in its concentration, but in its reflex action from the duodenum. We do not demand that bicarbonate of soda shall completely neutralize the acidity, because the quantity would have to be so large as to be really injurious. The solutions used by Bourget (1 per cent.) have a tendency to diminish the acidity only. By means of its above-named properties it not only overcomes the spasm at the pylorus, but also those in other parts of the stomach.

The 1 per cent. solution of sodium bicarbonate is administered not only at the height of acidity, but when the patient has pain or pyrosis. The solution is given regularly one to one and one-half hours after a light meal, and two to three hours after a heavy meal; besides that, at any time of the day or night when the patient is uncomfortable.

Mode of administration:

Sodii bicarbonatis purissimi	8.0-10.0
Sodii phosphatis sicci	4.0- 5.0
Sodii sulphatis sicci	2.0- 3.0

One powder in a quart of water taken ½-1 glass when necessary.

Or:

Sodii bicarbonatis purissimi	1.0
Sodii phosphatis sicci	0.4
Sodii sulphatis sicci	0.2

One powder in ½ glass warm water whenever necessary.

The treatment with alkalies can also be administered in the form of mineral water, preferably Karlsbad Muehlbrun, given warm, ½ pint on an empty stomach, and one hour before supper. This water does not agree with neurotic individuals, and a milder variety, like Celestin-Vichy, or Fachinger can be given instead.

Those alkaline waters which are very rich in gas should not be permitted, because of their property of distending the stomach and causing bleeding.

Francis W. Palfrey[64] used ox bile in fifty cases of ulcus ventriculi with good results. Although for a complete understanding of his reason for using bile we must refer to the original article, we will here give a short abstract.

It is physiologically a well-established fact (Cannon, Pawlow) that the chemical influence on the emptying of the stomach is exercised by the HCl on the gastric part, and the neutralizing power of the duodenum is brought about by the secretion of the duodenal mucosa, pancreatic juice and bile. A delay in emptying may as much depend on the failure of duodenum to neutralize the contents as on the disproportion in the acidity of the stomach. For this reason Palfrey gives ox bile in the dose of 0.25, three times a day, after meals, in order to stimulate the neutralizing power of the duodenum.

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[64] 64. Palfrey, Francis W.: The Administration of Ox-bile in the Treatment of Hyperacidity and of Gastric and Duodenal Ulcer. Am. Jour. Med. Sc., June, 1913, clxv, 796.

Glaessner[65] uses sodium glycocholate 0.2 with oil in capsules after meals, on the experimental basis that it neutralizes acidity.

The medicinal treatment outlined is also applicable to ambulatory cases. In these cases, when the autolavage property of the Carlsbad water in the morning does not suffice to give relief, we may wash the stomach out with alkaline water two or three times weekly for two or three weeks. We must be certain that there is no occult blood in the stomach or stools.

AFTER TREATMENT

The lasting effect and ultimate results of our treatment depend a great deal on continued observation of the patient. When discharged after five or six weeks, he should have a final thorough physical and chemical examination of the gastro-intestinal tract; and even when everything is found to be normal, the transition to a coarser diet (exercise diet) should be gradual. We gradually allow him boiled chicken, veal cutlets, lamb chops, steak well done and scrambled eggs; also different cooked fruits like peaches, prunes and pears in purée form. To the list of vegetables we add string beans, cauliflower and asparagus tips. Bread is allowed in a non-toasted form, but white, and one day old.

We dispense with all drugs, but advise an alkaline table water like Celestin or Fachinger; or, when expense is a factor, the above-mentioned 1 per cent. bicarbonate solution should be given in wine-glassful doses with meals.

Should the patient continue to show a tendency to hypersecretion, we should restrict salt to a minimum. Hydrotherapeutics in the form of a sponge bath or mild shower will prove useful. For those who can afford it, it is even advisable to take a month every year at a spa like Kissingen, Saratoga Springs or Karlsbad; or, if that is not possible, a home cure, consisting of taking mineral water one hour before breakfast and one hour before supper, should be maintained for a month.

TREATMENT OF HEMATEMESIS

Absolute rest in bed, flat on the back, foot of bed elevated, ice bag to the abdomen. In order to relieve the patient's anxiety, a small dose of morphin given hypodermatically (0.005 to 0.007) is useful. Light bandaging of the upper and lower extremities should be applied to obstruct the venous flow, but not to obliterate the pulse. Should the patient show considerable loss of blood we should try to replace the loss by rectal administration of Ringer's solution up to one pint, either by

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65. Glaessner: Eine neue Therapie der Hyperacid, Wien. klin. Wchnschr., 1913, No. 39.

enema or by the Murphy drop method. If this alone is not sufficient, try hypodermoclysis of normal saline solution, or intravenous normal saline, to which 10 to 15 drops of 1:1,000 epinephrin (adrenalin) chlorid is added.

No further stimulation is, as a rule, necessary; in fact, the weak pulse is even advantageous, as it allows a coagulum to form. Should, however, the pulse be fluttering and rapid, more stimulation is indicated. The most useful means is camphor-oil, 10 per cent., 5 c.c.

Hemostatics: if we have nothing on hand, we at once resort to a sterilized 10 per cent. saline solution, of which 5 c.c. should be given intravenously. According to many authors, this has worked when everything else failed. Gelatin in sterilized tubes 20 c.c. intramuscularly is also efficient. Blood-serum (horse) is also hemostatic. Lavage of the stomach with ice-cold water to stop hemorrhage has been advised by Fleiner; by Ewald with hot water; by Bourget with liquor sesquichloridi solution (1 per cent.).

We personally have had no experience with lavage, and feel that in a great majority of cases we can get along without it. However, where blood-clots stay in the stomach as an irritant, and cause excessive vomiting, lavage would be the proper procedure; we must emphasize in that event the advisability of cocainizing the pharynx with a 2 per cent. solution, in order to prevent straining or gagging.

In hemorrhage we should not allow even rectal feeding for twenty-four to forty-eight hours. On the second day we may administer 10 per cent. grape sugar solution per rectum. The rectal feeding begins on the third day, and is kept up to at least the sixth day, taking good care of the mouth to prevent parotitis. The rest of the treatment is like that outlined above, only to be continued for a longer time to prevent recurrence.

It is universally agreed that hemorrhages should be treated internally. But should they show a tendency to repetition in the future, then operation is indicated during the interval.

TREATMENT OF COMPLICATED ULCER

Those ulcers which do not yield to the above outlined treatment are undoubtedly complicated. At present when, with the aid of the Roentgen ray, the penetrating of callous ulcer, persistent hour-glass contraction, and adhesion to different organs can be diagnosticated earlier, we should not fail to take advantage of such means, and when found the case should be turned over to the surgeon.

The degeneration of ulcer into carcinoma certainly does occur (Aschoff has it that carcinoma was the primary condition). It is, however, a clinical fact that, in patients in whom the symptoms have persisted for years, carcinoma has developed.

From a therapeutic standpoint it is essential to diagnose the condition as early as possible, in order to turn the case over to the surgeon. Here Elsener's[66] observation, that if occult blood persists notwithstanding treatment carcinoma should be suspected, is a most valuable one. That the perforating gastric ulcer belongs to the surgeon need hardly be mentioned.

In treatment of benign stenosis of the pylorus due to ulcer, it is gratifying to find that Kemp[67] has accomplished the task of following up his eighty-seven cases of motility disturbance of the stomach of various degrees, in which pyloric stenosis is included, and found that internal treatment has a decidedly better influence on motility than surgical interference. His views concur fully with our observations.

It should be remembered that even stagnation of twelve to twenty-four hours' duration is not due to the thickening of the ulcer, but to the associated pylorospasm; the mechanical obstruction of the food is also due to the over-loaded stomach wall, while the musculature is still in a condition to be able to propel the food.

In such cases, as in acute ulcer, mental and bodily rest is essential: thorough lavage of the stomach twice daily, morning and evening, with alkaline solutions; rectal feeding for days, gradually testing as to whether the stomach can still expel the liquids introduced. Milk, preferably peptonized, in small quantities, is the food to be started with.

Just as soon as we find that the morning lavage is clear of the food from the day before, we should then use the lavage once only, in the morning, and gradually increase the food in quality and quantity, similarly to ulcus ventriculi, with the exception that the food should be given in purée form for months. These patients should be made to understand their condition, in order to observe dietary rules and rest, and just as soon as they have the slightest sensation of fullness or regurgitation, to report at once. When there are signs of stagnation, lavage of the stomach should be instituted and diet modified accordingly, until conditions improve.

We advise surgical treatment only if a conscientious attempt, as outlined above, has no effect.

OPERATIONS AND RESULTS OF OPERATIONS ON ULCUS VENTRICULI

It is not within the domain of this article to discuss the question of the kind of operation which is most useful. The valuable contributions to this subject by the Mayos, A. A. Berg, John B. Deaver and others.

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[66] Elsener: Lehrbuch f. Ulcus Krankh., 1911.

[67] Kemp.: Arch. f. Verdauungskr., 1913, No. 2.

throw a good light on the kind of operation most useful in individual cases.

We are considering the question chiefly from the internal standpoint, and we must always ask ourselves what are we to expect of the operation, and are the effects lasting? The symptoms of pain, hypersecretion, motility disturbances and occult blood, as pointed out above, when they do not yield to persistent internal treatment, demand surgical interference.

We know from experience that the symptoms that first and before all yield to surgical interference are the pain and bleeding. The next two most important symptoms, i. e., hypersecretion and disturbed motility, yield completely only in exceptional cases. In the majority of cases, as shown by Boas[68] and Kemp, the disturbance remains. This makes it imperative for us to observe the patient after the operation at certain intervals, to test the functions of the stomach, and to employ the Roentgen ray to see whether the new opening is acting. The Roentgen ray examination after an operation on an hour-glass stomach disclosed, in certain cases cited by Ewald, that the anastomosis did not include the upper part of stomach.

We must also bear in mind that patients suffering from ulcer of the stomach are predisposed to recurrences even after operation. Another complication arises through the fact that the acid gastric contents flow freely into the anastomosed intestine, causing occasional ulcus p. duodeni, or jejuni. The reason this is mentioned in detail is to show that the after-treatment must be kept up carefully.

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[68] Boas and Kemp: Berlin Gesellsch. f. Chir., 1913.

A SKIN REACTION INDICATIVE OF IMMUNITY AGAINST TYPHOID FEVER

*STUDIES IN TYPHOID IMMUNIZATION, III**

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It is generally accepted that the prophylactic immunization of human beings with living or dead preparations of the typhoid bacillus protects to a marked degree against typhoid fever. This protection is particularly demonstrable in segregated bodies like armies where immunized and non-immunized men are subjected to even chances of infection. In spite, however, of the convincing evidence of this protection by vaccination in the aggregate, we have as yet little evidence on the actual duration of any method of immunization, and no certainty as to security of an immunized individual. Firth,[1] to be sure, on the basis of the scientifically assembled statistics from the British Army in India, has ventured the statement that anti-typhoid immunizations may be expected to protect absolutely for two and a half years, with further evidence that partial immunity is enjoyed for four or five years. It would aid enormously in estimating the duration of immunity in general, in determining the most efficient method of immunization, and particularly in ascertaining the individual protection, if some reaction indicative of more or less perfect immunity could be devised.

Certain of the antibody tests, particularly the agglutination reaction and the reaction of fixation, are of recognized value in the diagnosis of typhoid fever; they are, however, of no certain significance as measuring actual resistance to typhoid infection. We have simply to mention that a high agglutination reaction affords no assurance of protection against a relapse in the disease, and on the other hand, that it is well recognized that those who have recovered from typhoid fever soon fail to give the reaction in the majority of cases, although they are usually protected for life from a recurrence of the disease. Bloch and Creuze[2] found a sensitizer (fixation reaction) in the serum of individuals immunized with Chantemesse's vaccine which appeared in from five to seven days following the initial injection and persisted in all cases for

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* Submitted for publication Nov. 13, 1913.

[1] Firth: A Statistical Study of Anti-Enteric Inoculation, Jour. Royal Army Med. Corps, 1911, xvi, 589.

[2] Bloch and Creuze: La sensibilisatrice dans le serum des subjets vaccinés contre la fièvre typhoïde, Compt. rend. Soc. de biol., 1912, lxxiii, 603.

at least four months; it was present in 83 per cent. of the treated patients for a year. They make no note of the presence of a similar antibody in recovered typhoids. Klien[3] has found the opsonic index of little value in indicating protection against typhoid fever. Moon[4] has obtained agglutinin reactions of varying intensity for at least a year after vigorous anti-typhoid immunization and appears justifiably sceptical as to their significance. Ardin-Delteil, Negre and Raynaud,[5] found the treatment of typhoid fever with vaccines increases the bactericidal power of the serum but not the agglutinins. Maverick[6] found a case that produced no agglutinins on repeated doses of vaccine.

The experimental results of Gay and Claypole on typhoid infection and immunization in rabbits, for the most part unpublished, show that the agglutination titer is of no value in measuring the *degree* of resistance to infection with the living organism. This is particularly true in immunization with sensitized cultures of typhoid bacilli, which give better protection but lower agglutinins than the untreated bacilli. This agrees in all details with the experimental and practical work with sensitized cultures in the hands of other investigators (Broughton-Alcock;[7] Ardin-Delteil, Negre and Raynaud;[8, 5] Garbat and Meyer[9]) who have uniformly obtained larger amounts of bactericidal substances but less agglutinins than when untreated cultures are employed.

It is evident, that the agglutination reaction, at least, is no measure of the grade or indeed of the existence of protection from typhoid infection. It may be that fixation or lytic tests would afford safer criteria, although they have the disadvantage of being more complicated.

SKIN REACTION

In our desire to find some method of indicating actual protection in human beings against typhoid fever, we have tried an adaptation of the v. Pirquet skin test with promising results.

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[3] Klien: The Opsonins in Typhoid Immunity. Bull. Johns Hopkins Hospital, 1907, xviii, 245.

[4] Moon: Experimental Immunity in Relation to the Agglutination Reaction in Typhoid, Jour. Am. Med. Assn., 1913. lx, 1764.

[5] Ardin-Delteil, Negre and Raynaud: Réchérches cliniques et expérimentales sur la vaccinotherapie de la fièvre typhoïde par le virus sensibilisé de Besredka, Ann. de l'Inst. Pasteur, 1913, xxvii, 644.

[6] Maverick: Typhoid Vaccination and the Widal Reaction, Jour. Am. Med. Assn., 1912, lviii, 1672.

[7] Broughton-Alcock: Vaccination for Typhoid by Living Sensibilized Typhoid Bacilli, Lancet, London, 1912, ii, 497.

[8] Ardin-Delteil, Negre and Raynaud: Réchérches sur les reactions humorales des malades atteints de fièvre typhoïde traités par la vaccin de Besredka, Comp. rend. Soc. de biol., 1913, v, lxxiv, 371; *ibid.*, Sur la vaccinotherapie de la fièvre typhoïde, Compt. rend. Acad. Sc., 1912, clv, 1174.

[9] Garbat and Meyer: Ueber Typhusheilserum, Ztschr. f. exper. Path., 1910. viii, 1.

The skin test has already been suggested as an additional method of diagnosis in typhoid fever, without, however, meeting with any general favor. Wolff-Eisner[10] could obtain no characteristic reaction in typhoid cases on intradermal inoculation of Ficker's Diagnosticum. Link[11] tried the skin reaction in nine cases with old concentrated bouillon cultures and obtained encouraging results in six of them. Most of these cases also showed a Widal reaction. Deehan[12] obtained a weak to moderate reaction in twelve cases of typhoid fever, whereas eight control cases showed none. Floyd and Barker[13] obtained positive results in nineteen out of thirty cases and none in eighteen controls, including two cases of paratyphoid infection. Chauffard and Troisier[14] find the reaction of little diagnostic value as it is also given, though in less degree, by control cases.

TECHNIC OF SKIN TEST EMPLOYED

The method of applying the typhoid skin test is a modification of the von Pirquet method of tuberculin testing as already introduced by one of us as a test for immunity against cow-pox vaccine.[15] It consists in producing an abrasion of uniform size and depth designed to cut just through the epidermis of the arm without drawing blood. This abrasion is produced by a complete twist of a chisel with straight edge (measuring 2.25 millimeters) and square corners supplied on specification by the Cutter Analytic Laboratory and so tempered as to resist sterilization by burning alcohol. The skin is prepared by cleansing with 95 per cent. alcohol. Various preparations of the typhoid bacillus have been tried with varying success, and the one actually chosen as the most efficient is prepared in a manner similar to the one employed in producing Koch's old tuberculin: 250 c.c. of 5 per cent. glycerin bouillon was inoculated with *B. typhosus* (Dorset Army Strain No. 5) and incubated for five days. It was then reduced without filtration to one-tenth of its original volume by evaporation over a 56 acetone bath for about eight hours. A control solution of sterile 5 per cent. glycerin bouillon was evaporated at the same time to equivalent volume.

Two uniform abrasions are produced on the upper arm or fore-arm of each patient tested, and the control solution gently rubbed into the inner spot with a sterile toothpick, and the "Typhoidin" solution similarly applied to the outer spot. The reactions are observed six and twenty-four hours later, and more rarely at subsequent periods. In a very few instances the six-hour period shows in positive cases an accelerated reaction which diminishes or actually disappears within twenty-four hours. Not infrequently, however, a positive test persists for a week. In the majority of cases the control spot shows a 2 mm. healed abrasion not surrounded by an areola; in the minority of cases a slight zone of traumatic or irritative redness may occur about the abrasion. In these latter cases when there is a positive reaction in the "Typhoidin" spot there is no difficulty in noting and measuring the differences between its areola and the control redness. We have arbitrarily chosen a difference of 2.5 mm. between the two areolas as indicative of a positive reaction. The positive spot measures from 4 to 12 mm. in extreme diameter and is usually somewhat indurated and frequently clearly demarcated. In negative cases there is the same reaction or absence of reaction in the control and "Typhoidin" spots. In the routine examination, as a rule, twenty or more cases representative of the various categories were tested at a time, after history-taking, and to avoid prejudice, the nature of the reaction decided on before the history was referred to.

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[10] Wolff-Eisner: Die Opthalmo- und Cuti-diagnose der Tuberculose, Wurzburg, 1908.

[11] Link: Ueber Hautreaktionen bei Impfungen mit abgetoteten Typhus, Paratyphosus B, and Koli-Kulturen, München. med. Wchnschr., 1908, lv, 730.

[12] Deehan: The Typhoid Cutaneous Reaction, Univ. Penn. Med. Bull., 1909, xxii, 6.

[13] Floyd and Barker: The Typhoid Cutaneous Reaction, Am. Jour. Med. Sc., 1909, xxxviii, 188.

[14] Chauffard and Troisier: Réproduction expérimentale des taches roseés lenticulaires., Compt. rend. Soc. de biol., 1909, lxvi, 519.

[15] Force: The Skin Reaction After Cow-Pox Vaccination: a Possible Aid in Public Health Administration, Cal. State Jour. Med., July, 1913; *ibid.*, A Test for Immunity Against Cow-Pox Vaccination. (In press.)

We have examined in all 124 cases by this method, repeating the test in a few cases where there was doubt in the result. We may consider first the results of the test in those cases that gave a satisfactorily detailed and designated history of typhoid fever as individuals in whom there is presumptive evidence of protection against typhoid fever.

TABLE 1.—Cases Giving a Definite History of Typhoid Fever

No.	Patient	Interval Years	Skin Test	Remarks
98	W. H. S.......	41	Positive	
10	W. G. H.......	33	Positive	
117	J. G. O........	20	Positive	
5	K.	14	Positive	
63	E. S.	10	Positive	
40	F. D.	10	Positive	
2	J. T. H........	10	Positive	
1	T.	10	Positive	
30	M. C.	10	Positive	
28	T. C. B........	9	Positive	
8	G.	8	Positive	
86	P. A. R........	8	Positive	
29	T. D.	8	Positive	
17	M. K.	8	Positive	
20	R.	7	Positive	
13	A. L. H........	7	Positive	
11	O. H.	6	Positive	
3	M. L. K........	4	Positive	
4	F. J.	3	Positive	
126	J. T. F........	16*	Negative ...	Suffering from neuritis.
33	D. G. M.......	4½*	Positive	Widal negative 1-25.

* Months.

As is seen from this table, twenty-one cases with a definite history ranging from 41 years to 4½ months previously were examined, and of these one only was negative. In other words, in the cases presumably protected against recurrence of typhoid fever, 95 per cent. gave a positive skin reaction.

We may tabulate at this point the results obtained in seven cases in which a history suggesting typhoid fever was obtained without report of a definite diagnosis to this effect. It may be remarked that in two of these cases the history was obtained before the skin test was applied; in the other cases, the history was obtained by further inquiry in cases chosen as controls that showed an unexpectedly positive reaction (Table 2).

TABLE 2.—Cases with Doubtful History of Typhoid Fever

No.	Patient	Interval Years	Skin Test	Remarks
44	O. R. G.	21	Positive	History of "malaria."
75	B. P. D.	13	Positive	Severe intermittent: delirious; mother and sister affected.
45	H. H. S.	12	Positive	Eight-day fever at 9 yrs.
96	A. P.	10	Positive	Intermittent fever over six weeks.
77	L. B. T.	6	Positive	Ambulatory; delirium: 3 weeks; in tropics.
79	E. M.	1	Doubtful	"Malaria."
102	J. A. D.	12	Positive	History of "malaria."

We may now consider the individuals tested as controls, from whom no history of an illness diagnosed as typhoid fever, or, on questioning, resembling typhoid fever, could be elicited. As the individuals who kindly volunteered for this test were for the most part medical students, an intelligent cooperation in history taking has been assured.

TABLE 3.—Cases with No History of Typhoid Fever (Controls)

No.	Name	Reaction	No.	Name	Reaction
32	H. A. T.	Negative.	50	R. S. B.	Negative
14	Mrs S.	Negative.	53	H. P. H.	Negative
22	O. A. S.	Positive	16	B.	Negative
6	B.	Negative	78	S.	Negative
7	S.	Negative	80	R. H. H.	Negative
9	W. G. S.	Negative	83	P. F. A.	Negative
73	F. G. L.	Negative	84	Mrs. R.	Negative
72	J. A. O.	Negative	82	A. S.	Doubtful
71	H. A. F.	Negative	88	W. C. F.	Doubtful
70	W. E. C.	Negative	94	H. H. M.	Negative
69	L. M. N.	Positive	92	D. R. M.	Negative
67	R. R. N.	Negative	103	M. L. C.	Negative
66	C. L.	Negative	108	E. R.	Negative
64	L. M. B.	Negative	107	O. M.	Negative
58	F. P.	Positive	109	Z. Y. K.	Negative
35	R. S. A.	Positive	101	J. E. H.	Negative
37	W. C. S.	Negative	97	E. H.	Negative
74	D. C.	Negative	95	L. L. C.	Negative
46	J. A. J.	Negative	100	D. S.	Negative
47	E. C.	Negative	110	L. W.	Negative
49	E. W. S.	Negative			

As is evident from the table, of the forty-one negative control cases tested, thirty-five or 85 per cent., gave a negative "Typhoidin" reaction, two were marked as doubtful, and four only, or 9 per cent., were distinctly positive. In view of the contrast between these cases and those with a positive typhoid history, and the apparent relative reliability of the reaction in the positive cases, the question naturally arises as to the possibility of a mild or abortive attack of typhoid fever in the 9 per cent. of reactors with a negative history.

Our results to this point would seem to establish beyond doubt the value of our cutaneous test as differentiating with a high degree of accuracy between those who have had typhoid fever and those who have not. But as has already been mentioned, our principal interest in devising this test has been its use as an indicator of protection in those who have been artificially immunized against typhoid fever. Inasmuch as it does occur in recently vaccinated individuals, we trust it may eventually be relied on as truly indicating protection, may be used to test the relative immunizing values of different vaccine preparations, and may be currently employed in vaccinated individuals to mark the period when re-vaccination should be recommended.

TABLE 4.—PATIENTS VACCINATED AGAINST TYPHOID (ARMY METHOD)

No.	Name	Interval Years	Reaction
135	A. D. P........	4½	Positive.
111	J. I. M........	4¾	Positive.
113	M. F. D.......	3	Positive.
127	J. W.	2	Negative.
130	F. A. S........	2	Negative.
120	S. G.	2	Negative.
132	L.	2	Positive.
134	L. L. B........	1¾	Positive.
123	A. F. W.......	1½	Negative.
125	W. J. F........	1½	Negative.
129	A. C. W........	1—2*	Negative.
116	L. L. F.......	11½*	Positive.
119	J. P. K........	11*	Positive.
133	F. C.	9	Positive.
118	R. A. G.......	8*	Positive.

* Months.

Our tests in immunized individuals are assembled in Tables 4, 5 and 6, which are segregated in accordance with the method of vaccination employed, and arranged in accordance with the intervals that had elapsed between vaccination and the test.

The Army method consists, as is well known, in the inoculation of three doses of a killed culture of a mild and long cultured strain of *B. typhosus,* given at intervals of a week or ten days. The doses are

TABLE 5.—PATIENTS VACCINATED WITH CUTTER VACCINE

No.	Name	Interval Years	Reaction
34	G. F. R.......	4	Positive.
19	F. L. K.....	15*	Positive.
140	H.	1	Positive.
141	K.	1	Negative.
142	S.	1	Positive.
143	Dr. S.	1	Positive.

* Months.

TABLE 6.—PATIENTS VACCINATED AGAINST TYPHOID WITH SENSITIZED VACCINE (METHOD OF GAY AND CLAYPOLE)

No.	Name	Interval Months	Reaction
31	L. R. B........	8	Positive.
25	E. J. C........	8	Positive.
24	J. N. F........	8	Positive.
23	F. P. G........	8	Positive.
21	E. S. B........	8	Positive.
34	F. C. C........	8	Positive.
26	G. Y. R........	7	Positive.
18	A. F.	7	Positive.
91	E. W. F.......	7	Positive.
81	J. M.	6	Positive.
85	O. S. C........	6	Positive
39	W. D. H.......	6	Positive
41	M. G. W.......	6	Positive
38	D. H. H.	6	Positive
43	L. W. B.......	6	Positive
42	K. P. F.......	6	Positive
54	W. A. B........	6	Positive.
61	C. D. H........	5	Positive.
51	M. S.	5	Positive.
48	M. A.	5	Positive.
52	W. H.	5	Positive.
68	W. G. R........	4	Positive.
27	G. L. G........	3	Positive.
76	R. P.	3	Positive.
15	W. A. S........	1	Positive.
105	E. S.	3*	Positive.
106	E. W.	3*	Negative.
90	S.	3*	Positive.
93	E. R. Z........	2*	Positive.
99	F.	2*	Positive.
104	J. S.	2*	Positive.
87	F. G.	10†	Negative‡
89	M. B.	10†	Positive§
56	E. F. M.......	1*	Negative¶

* Weeks. † Days. ‡ Widal positive 1-50. § Widal doubtful 1-50. ¶ Widal negative 1-25.

usually 250, 500, and 500 millions of bacteria. The reaction produced is now reported to be mild. Immunization with the Cutter vaccine is similar to the Army method, but from evidence that has come to us the marked or severe reactions are not inconsiderable in number.

The vaccine at present furnished by Gay and Claypole has been utilized in vaccinating over 900 individuals, for the most part University students, and its freedom from untoward effects has been reported by Force.[16] The full report of the method of preparation and the experimental study by which the superiority of this vaccine over the ordinary vaccine is evidenced, will soon be published in sequence to a series of studies that is now appearing in this journal.[17] It will suffice at this point to state that it is a preparation of sensitized (Besredka) typhoid bacilli precipitated and sterilized by alcohol, ground in an agate mortar, weighed, and suspended in 0.5 per cent. carbolated saline solution. Three injections of 1/16 mg. (= 500,000,000 bacteria) are given at *two- or three-day* intervals. A further perfectioning of the method from the standpoint of reactions and immunizing value is in progress.

A study of these tables shows that of tweny-one individuals in the army and in civil life vaccinated with killed cultures of typhoid bacilli (Army or Cutter vaccine) at intervals of from eight months to four and three-quarter years previously, fourteen gave a positive skin reaction. All the cases vaccinated by the Gay-Claypole vaccine at from one to eight months previously gave positive reactions (25 cases). Of nine cases vaccinated three weeks or less previously, three did not react. In the later cases immunity doubtless was not fully established. Owing to the differences in point of time elapsed, no comparisons of the relative efficiency of the two methods can be made or is intended.

Agglutination tests (Widal) have been noted in a few instances. A complete comparison between the Widal test and the skin reaction in a large number of cases would be of interest, although the unreliability of the agglutination titer as indicative of immunity has been already noted. This is particularly true in the case of employment of sensitized vaccines, although the latter method gives indications of perfect immunity up to eight months, as judged by the skin test.

Obviously, it is too early to refer to the skin test as of more than presumptive value in indicating typhoid immunity. An extended series of observations over a long period of time checked by morbidity statistics in large bodies of individuals is necessary before we can assume that the test is of certain prognostic significance. As a working basis, however, we feel justified in recommending re-vaccination in individuals who at any time subsequent to a month after vaccination fail to give a positive skin reaction.

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[16] Force: Institutional Vaccination Against Typhoid Fever, Am. Jour. Pub. Health, 1913, iii, 750.

[17] Gay and Claypole: THE ARCHIVES INT. MED., xiii, No. 1.

We wish to thank Lieutenant-Colonel E. B. Frick, Major Roger Brooke, and Captain W. B. Snow of the Medical Corps, United States Army, stationed at the Lettermann General Hospital, for allowing us to examine and report on soldiers under their care who had been vaccinated previously by the army method.

CONCLUSIONS

A preparation of the typhoid bacillus ("Typhoidin") in all respects similar to Koch's old tuberculin produces a clear-cut cutaneous reaction by the von Pirquet method in 95 per cent. of cases that have recovered from typhoid fever (20 cases positive out of 21). Two of the cases had suffered from the disease forty-one and thirty-three years before, respectively. The reaction is negative in 85 per cent. of individuals without history of typhoid fever (41 cases tested). The 9 per cent. of these supposedly control individuals that gave a distinct positive reaction may be suspected of having had a mild and undiagnosed attack of typhoid fever. Of fifteen individuals vaccinated by the Army method from four and three-quarter years to eight months previously, nine gave a positive skin reaction. Twenty-five individuals vaccinated by the Gay-Claypole sensitized vaccine for from one to eight months previously gave uniformly a positive reaction.

No comparison is intended in the efficacy of the two methods, although it is suggested that the skin test may eventually be used for such a determination. It is further suggested that the test is of presumptive value in indicating protection against typhoid fever whether acquired by recovery from the disease or by artificial immunization against the disease. The test may eventually be used as an indication for re-vaccination in the individual case.

THE INFLUENCE OF LITHIUM AND ATOPHAN ON THE URIC ACID EXCRETION OF A GOUTY PATIENT *

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Recent work of Folin and Lyman[1] points to the conclusion that gout is caused by an accumulation of uric acid in the blood with a subsequent deposition of this in an insoluble form in the various tissues of the body, particularly in the joints and synovial membranes. The retention and consequent accumulation is due to a deficient and restricted power of the kidneys. By means of the new colorimetric method of Folin and Denis[2] these investigators have analyzed the blood from a large number of patients suffering from gout and have found the uric acid content higher than in normal individuals; in these patients the blood was frequently found to have reached the saturation point for this compound, namely, 4 mg. in 100 c.c. of blood. Atophan (2-phenylquinolin-4-carbonic acid) caused a decrease in the amount of uric acid in the blood and a corresponding increase in the uric acid eliminated. Nicolaier and Dohrn,[3] Plehn[4] and Haskins[5] have shown that this increase is followed by a sudden decrease, and for some days the output is less than during the period preceding the administration of the atophan. The conclusion is that atophan removes the uric acid from the blood by increasing the secreting power of the kidneys, but it does not mobilize the deposited urates.

In view of these results of Folin and Lyman the problem of finding a solvent for the uric acid in the blood of gouty patients no longer interests us. In whatever form this exists it can be removed by stimulating the kidney functions. We may speculate on a future when there shall be no more gout; a periodic dose of atophan will remove the accumulated uric acid and thus prevent the deposits which are now a conspicuous feature of this disease. But the problem of removing these deposited urates, of helping those who are now suffering, as well as of determining wherein the kidneys fail in fulfilling their normal functions, remains unsolved.

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*From the Department of Home Economics, University of Missouri.

*Submitted for publication Nov. 24, 1913.

1. Folin and Lyman: Jour. Pharm. and Exper. Therap., 1913, iv, 539.
2. Folin and Denis: Jour. Biol. Chem., 1913, xiii, 469.
3. Nicolaier and Dohrn: Deutsch. Arch. f. klin. Med., 1908, xciii, 331.
4. Plehn: Deutsche. Med. Wchschr., 1912, No. 3.
5. Haskins: Jour. Pharm. and Exper. Therap., 1913, v, 63.

Formerly solutions of lithium salts constituted one of the most used remedies for gout and rheumatism. The rationale of this treatment was based on some early work of Ure,[6] who found that uric acid is much more soluble in solutions of lithium salts than in the corresponding salts of potassium and sodium. The assumption was that lithium introduced into the organism dissolved the uric acid and made it more easily excreted. Later work showed that the reaction which took place so readily in the test-tube when lithium and uric acid were the only reacting substances did not occur when salts of phosphoric acid, in similar concentration to those in the blood, were present; instead, the lithium formed an insoluble compound with the sodium phosphate. Lithium as a remedy for gout fell into disrepute.

There is a paucity of data in the literature relative to the effect of lithium on the uric acid elimination. All the evidence which I have been able to find pertaining to the therapeutic effect of lithium in gout has been the result of test-tube experimentation. It is conceivable that those changes which take place in the test-tube do not occur when the lithium is introduced into the body. In the blood-serum the salts are dissociated into their ions, and we have to deal only with sodium, calcium and potassium ions and with uric, chloric, carbonic, phosphate and sulphate ions existing side by side. We have no evidence that lithium in the body will form insoluble compounds with any of the ions present. Furthermore, a solution of lithium citrate when added to filtered pig's blood causes no precipitation of the inorganic constituents.

The tophi of the joints are made up largely of sodium and potassium urates with a small proportion of calcium urate. The problem, then, of removing these from the body is getting the sodium, potassium and calcium urates into solution. Because of the low atomic weight of lithium, a comparatively small amount is required to produce a given reaction. This, then, would seem the ideal cation to introduce into the body to bring about the desired solution. Experiments[7] have been reported in which cartilage impregnated with sodium urate has been suspended in aqueous solutions of the carbonates of lithium, potassium and sodium; at the end of forty-eight hours the cartilage suspended in the lithium solution was restored to its normal condition, the cartilage in the potassium solution was much acted on, while that in the sodium was unaffected. Luff[8] aimed to determine the solubility of sodium biurate in artificial blood-serum to which he added different proportions of lithium carbonate and lithium citrate, as well as other inorganic salts. The artificial blood-serum consisted of 0.5 gm. of sodium chlorid, 0.2

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[6] Ure: Med. Times, 1844, xi, 145.

[7] Garrod: Quoted from Luff: Gout, p. 181, 1899

[8] Luff: Gout, p. 183, 1899.

gm. of sodium bicarbonate and 100 c.c. of distilled water; this, Luff maintained, represented the blood-serum so far as the saline ingredients are concerned. Neither of the lithium salts increased the solubility of the solution for sodium biurate. But the conditions in neither group of experiments were comparable with those existing in the body. It is not possible to surround the tophi with a medium consisting only of lithium salts; nor is the blood-serum such a simple mixture as Luff's artificial serum would indicate. In the latter experiments the failure of the sodium urate to go into solution has been attributed to the preponderance of the sodium ions in the serum. While it is true that any two salts susceptible of dissociation, which contain an electric ion in common, mutually diminish each other's solubility, the converse of this proportion has been found to be true, and salts possessing no electric ion in common may mutually increase each other's solubility in a fluid. The ever-changing ionic environment surrounding the urate deposits in the body was not duplicated in Luff's experiments. It is not improbable that the deposited urates may be slowly dissolved by the introduction of lithium ions.

If, in the past, substances capable of causing a solution of the deposited urates had been introduced into the gouty body, the evidence of such a solution would not have been forthcoming, for in this disorder it has been shown that the blood is already saturated with uric acid and the kidneys are unable to relieve the condition. Since we now have a substance which makes the kidneys more permeable to uric acid, it seemed advisable to determine if lithium has any influence on the urate deposits in those suffering from gout. It was in order to test this point that the investigation here reported was undertaken.

The patient, a woman of 55, has been a sufferer from chronic gout for at least ten years. The disease is apparently well advanced, for the joints of the fingers, toes and knees show marked deposits. Throughout the investigation the patient was kept on a liberal but purin-free diet. The uric acid elimination was taken as the criterion of the solution of deposited urates. The uric acid analyses were made according to the method of Folin and Denis.[2]

The accompanying table gives the data of the investigation.

It will be noted that the uric acid elimination (0.26 gm.) during the preliminary period, that is, before any atophan was taken, was somewhat lower than that of normal individuals, which according to Magnus-Levy[9] is from 0.3 to 0.6 gm. in twenty-four hours. Atophan caused an increase of 72 per cent. in the first excretion. Following the atophan (Period 3) the output was slightly lower than that of the former period. These results are comparable with those of other investigators and have been explained on the theory that the atophan caused a depletion of the uric acid of the blood. The introduction of 15 gr. of lithium citrate (5 grains three times a day) during a time when no atophan was being given did not influence the uric acid output (Period 4). Atophan (Period 5) was again given, together with lithium. The average output

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[9] Magnus-Levy: Am. Jour. Med. Sc., 1910, cxl, 625.

EXCRETION OF URIC ACID AS INFLUENCED BY ATOPHAN AND LITHIUM CITRATE

Period	Date	Urine Volume c.c.	Uric Acid Gm.	Atophan Gm.	Lithium Citrate Grains	Uric Acid Average Gm.
	7/14	1.545	0.262	......	.....	
1	7/15	960	0.297	......	.....	0.26
	7/16	1,600	0.232	......	.....	
2	7/18	2,255	0.491	3 × 1.5*	.....	0.455
	7/19	2.120	0.410	3 × 1.5	.....	
	7/20	1,635	0.245	1 × 0.5	.....	
3	7/21	1,440	0.243	......	.....	0.242
	7/22	1,445	0.238	......	.....	
	7/24	1.615	0.189	......	3 × 5†	
4	7/25	1,515	0.313	......	3 × 5	0.244
	7/26	1.935	0.255	......	3 × 5	
	7/28	1,660	0.22	......	3 × 5	
	7/29	1,796	0.38	3 × 0.5	3 × 5	
5	7/30	2,245	0.345	3 × 0.5	3 × 5	0.311
	7/31	1,490	0.257	3 × 0.5	3 × 5	
	8/1	2,580	0.304	3 × 0.5	3 × 5	
	8/2	2,005	0.282	3 × 0.5	3 × 5	
6	8/3	1,380	0.270	3 × 0.5	.....	0.27
	8/4	1.395	0.269	3 × 0.5	.....	
	8/5	1,915	0.381	3 × 0.5	6 × 5	
7	8/6	2,325	0.453	3 × 0.5	5 × 5	
	8/7	2,365	0.386	3 × 0.5	4 × 5	0.42
	8/8	2,175	0.439	3 × 0.5	5 × 5	
	8/9	2,180	0.431	3 × 0.5	5 × 5	
	8/16	....	....	3 × 0.5	4 × 5	
8	8/17	....	....	3 × 0.5	4 × 5	
	8/18	1,190	0.370	3 × 0.5	4 × 5	0.37

* One and one-half grams three times a day.

† Five grains three times a day.

for five days was 27 per cent. higher than during the time (Period 4) when no atophan was being given. This increase, we may assume, was due to the endogenous uric acid which had piled up in the blood since the former dose of atophan, eight days previous. During Period 6 the atophan was continued but the lithium was discontinued; there was a slight decrease in the elimination—from 0.31 gm. to 0.27 gm.; but as this period lasted only two days I attach no significance to the slight drop. During the following five days (Period 7) more frequent doses of lithium (from 20 to 30 grains a day) together with atophan were given. The increase in the elimination—55 per cent.—was unmistakable; it very nearly equaled the output during the first atophan period when the blood was presumably saturated with uric acid. After a week of rest, while the patient was still on a purin-free diet, another trial was made. As in the previous tests atophan and the more frequent doses of lithium were given. Only one analysis was made, on the third day. The output, 0.37 gm., compares with that of the preceding period. The smaller quantity of lithium apparently had very little, if any, influence on the uric acid elimination, but the larger amount caused such an increase as to lead us to believe that the blood had again become saturated with uric acid.

In the absence of another reasonable explanation, the increase in the uric acid elimination when both atophan and lithium were being taken must be attributed to a solution of some of the deposited urates. The output at this time corresponds to the excretion after the first dose of atophan when the blood was presumably saturated. The fact that atophan had been given for seven successive days before the larger quantity of lithium would preclude the possibility that the blood had again become saturated with endogenous uric acid. But conclusions should not be drawn from a single series of tests with one patient.

It is impossible to continue this research for some time at least. Therefore these data are reported with the hope that they will stimulate further investigation of this subject.

COMPARATIVE STUDY OF PHENOLSULPHONEPHTHALEIN ELIMINATION AND THE INCOAGULABLE NITROGEN OF THE BLOOD IN CARDIORENAL DISEASES *

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INTRODUCTION

Since its introduction by Rowntree and Geraghty,[1] the phenolsulphonephthalein test has to a great extent superseded all other tests of this class as an index of renal efficiency. The excretory ability of the kidney is measured by injecting a definite foreign substance and noting the amount eliminated within a definite time. Since Provost and Dumas[2] found large quantities of urea in the blood of nephrectomized dogs, and since Babington working with Bright[3] noted the large amount of urea in the blood of a nephritic, however, attention has been directed to the incoagulable nitrogen of the blood with the idea that its determination would indicate the permeability of the kidney to normal or abnormal nitrogenous metabolic products.

A large number of observers[4] have studied the urea of the blood and have noted a decided increase in patients with uremia, eclampsia, acute mercury poisoning and cholera.

Strauss[5] was the first to study systematically the blood in nephritis. He collected a large amount of data and found that in nephritis there was generally an increase of the incoagulable nitrogen, which he regarded as an evidence of renal insufficiency.

Owing to the variety of methods of precipitating the proteins and particularly of determining the urea nitrogen, markedly varying results have been obtained by various authors. Recently Folin and Denis[6] have devised a colorimetric method for estimating urea and nitrogen which requires but little blood, and in their hands has been very accurate. We have used this method in the present study.

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* From the Department of Internal Medicine, University of Michigan.

* Submitted for publication Sept. 31, 1913.

[1] Rowntree and Geraghty: Jour. Pharm. and Exper. Therap., 1910, i, 579.

[2] Prevost and Dumas: Quoted by Schöndorff, Arch. f. d. ges. Physiol., Pfluger's, 1899, lxxiv, 307.

[3] Bright, R.: Guy's Hosp. Rep., 1836, i, 360.

[4] For an historical summary of this work with references, see Schöndorff: Arch. f. d. ges. Physiol., Pfluger's, 1899, lxxiv, 307.

[5] Strauss, H.: Die chronische Nierentzündungen in ihrer Einwirkung auf die Blutflüssigkeit und deren Behandlung, Berlin, A. Hirschwald, 1902.

[6] Folin, O., and Denis, W.: Jour. Biol. Chem., 1911, xi, 527.

The French, headed by Widal, Javal and Ambard, have used the hypobromite method to determine the "urea," as they term it, in the blood, and from these determinations on a large number of patients they have drawn very definite conclusions, especially in regard to the prognostic significance of increased amounts of urea in the blood. While this method is chemically imperfect, yet because of its extensive use by the French, we have used it in conjunction with the determinations by Folin's method.

The objects of the present study were to determine what relation, if any, existed between phthalein excretion and the incoagulable nitrogen of the blood; whether the relation of urea nitrogen to total nitrogen was of any significance; to what extent the hypobromite method could be depended on; and what diagnostic or prognostic value may be attributed to an increase in the incoagulable nitrogen of the blood.

METHODS

The phthalein test was done by intramuscular injection according to the original technic of Rowntree and Geraghty,[1] and the values given are percentages of excretion over a two-hour period.

The determination of urea nitrogen and the total incoagulable nitrogen, according to the method of Folin and Denis,[6] was briefly as follows:

Blood was obtained from the median basilic vein by puncture and allowed to flow into a vessel containing a little powdered potassium oxalate to prevent coagulation. The blood was precipitated with chemically pure, acetone-free methyl alcohol and the filtrate reprecipitated with an alcoholic solution of zinc chlorid. Samples of this second filtrate were taken for analysis. For the nitrogen determination the alcohol was evaporated and the residue decomposed by heating with sulphuric acid and potassium sulphate, a miniature Kjeldahl. This was then made strongly alkaline and the ammonia aspirated by an air-current into a dilute solution of hydrochloric acid which was Nesslerized, and the amount of nitrogen estimated by comparison in a Doboscq colorimeter with the color of a Nesslerized standard solution of ammonium sulphate. For the urea determination the alcohol was evaporated by aspirating an air-current through it and the urea hydrolyzed by heating with acetic acid and potassium acetate at a temperature of 155 C. (311 F.). After hydrolysis the solution was made alkaline, the ammonia aspirated and the nitrogen estimated as above. This portion also contains the preformed ammonia of the blood and is designated as the urea-ammonia fraction. Separate determinations of ammonia were not made, nor has any account been taken of other non-precipitable nitrogenous bodies in the blood.

The advantages of Folin's method are its accuracy and delicacy and the fact that but little blood is needed. The disadvantages from a clinical standpoint are that it is technical, time-consuming and requires considerable care and experience before accurate results can be obtained. All analyses were made in duplicate and the determinations were not regarded as satisfactory unless the colorimetric readings checked within 5 per cent. Farr and Austin[7] have experienced difficulty in obtaining concordant results in the urea determination, and we have also had this trouble, it often being necessary to run five or six samples before getting a check. We have no explanation to offer for this difficulty, but because of it we have less confidence in our figures for the urea-ammonia nitrogen than in those for total incoagulable nitrogen. In the table the results obtained are expressed as incoagulable nitrogen per 100 c.c. of blood, urea-ammonia nitrogen per 100 c.c. of blood, and from these figures is computed the urea[8] per 100 c.c. of blood and the percentage relation of urea-ammonia nitrogen to total incoagulable nitrogen.

For the determination of nitrogen by hyprobromite, a slight modification of the method used by Widal[9] was employed, and in conformity with the French workers the values obtained are expressed as urea per 100 c.c. of blood. The method was as follows:

Blood was obtained as for the Folin method, and of this 10 c.c. were added, drop by drop, to 115 c.c. of chemically pure, acetone-free methyl alcohol, stirred well and filtered through a dry filter. The filtrate at this point was not treated with zinc chlorid as in the Folin method, and this may account for some variations in results which will be mentioned later. One hundred c.c. of the alcoholic filtrate (corresponding to 8 c.c. of blood) was then evaporated at a low temperature on the water-bath almost to dryness. The residue was taken up with a few cubic centimeters of distilled water, washed carefully into a ureometer tube of the Yvon type, decomposed with sodium hypobromite, the volume of liberated nitrogen determined with regard to temperature and the equalization of pressure, and the amount of urea calculated from the volume of nitrogen found. Owing to the amount of blood required in this estimation, duplicate analyses could be made in only a few instances, and therefore the results could not be checked. The advantages of the hypobromite method are that it is simple and can be quickly done. The analyses by the two methods were made on blood taken at the same time.

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[7] Farr, C. B., and Austin, J. H.: Proc. Soc. Exper. Biol. and Med., 1913, x, 169.

[8] Since the ammonia nitrogen of the urea-ammonia fraction is an unknown variable the amount of urea computed from these figures is somewhat in excess of the actual amount.

[9] Widal, F.: Le mouvement medical, 1913, i, 1.

NORMAL VALUES

The normal phthalein elimination in two hours is generally given at from 60 to 85 per cent. of the amount injected, with the first figure as the lower limit.

When we come to consider the amount of incoagulable and urea nitrogen normally in the blood, we are confronted by a great variety of figures, depending on the way in which the proteins of the blood were precipitated and the methods which were used for the urea determination. Schöndorff,[10] who precipitated the proteins with phosphotungstic acid and determined the urea by the method devised by him, gives 61 mg. per 100 c.c. of blood as the normal urea content. Strauss[5] precipitated with acetic acid and found 20 to 35 mg. incoagulable nitrogen per 100 c.c. of blood as normal, of which 50 to 75 per cent. was urea nitrogen. Von Jaksch,[11] who precipitated with phosphotungstic acid, found the urea nitrogen to be 23 to 28 mg. per 100 c.c. of blood. Obermayer and Popper,[12] after removing the proteins with acetic acid, found the normal incoagulable nitrogen to be 36 mg. per 100 c.c. of blood, and, after fractionating with tannic and phosphotungstic acids, found the urea nitrogen to be 18 mg. per 100 c.c. of blood. Hohlweg[13] precipitated with acetic acid and monocalcium phosphate and found the normal incoagulable nitrogen per 100 c.c. of blood to be 51 mg., of which 31 mg. was urea nitrogen. Foster[14] removed the proteins by precipitation with alcohol and found the incoagulable nitrogen per 100 c.c. of blood in non-nephritics to vary from 33 to 54 mg., of which the urea nitrogen was 20 to 39 mg.; Strauss,[15] in a more recent publication, precipitated the proteins according to Folin and Denis, and gives 30 to 40 mg. per 100 c.c. of blood as the normal amount of incoagulable nitrogen. Folin and Denis,[16] using their own method, give the incoagulable nitrogen per 100 c.c. of blood at from 22 to 26 mg., of which 50 per cent. is urea nitrogen. Oszacki[17] precipitated with uranyl acetate and gives 42 mg. per 100 c.c. of blood as the normal amount of incoagulable nitrogen, of which 50 per cent. is urea nitrogen. While Farr and Austin,[7] using Folin's method, found that patients showing no evidence of kidney insufficiency, showed a variation in incoagulable nitrogen of 16 to 43 mg. per 100 c.c. of blood, of which 50 to 60 per cent. was in the urea-ammonia fraction. Folin and Denis[16] also emphasize the fact that as soon as any other than perfectly healthy persons are considered, or when any sort of clinical material is taken, higher values are obtained, even though there are no evidences of renal disease.

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[10] Schöndorff: Arch. f. d. ges. Physiol., Pflüger's, 1899, lxxiv, 358.

[11] Von Jaksch: Quoted by Hohlweg: Deutsch. Arch. f. klin. Med., 1912, civ, 216.

[12] Obermayer and Popper: Ztschr. f. klin. Med., 1911, lxxii, 332.

[13] Hohlweg: Deutsch. Arch. f. klin. Med., 1912, civ, 216.

[14] Foster, N. B.: The Archives Int. Med., 1912, x, 414.

[15] Strauss, H.: Ztschr. f. Urol., 1913, vii, 287.

[16] Folin, C., and Denis, W.: Jour. Biol. Chem., 1913, xiv, 29.

[17] Oszacki: Ztschr. f. klin. Med., 1913, lxxvii, 1.

In dealing with the amount of incoagulable nitrogen in the blood, there are several factors to be considered, among which are the diet of the patient and the time of day at which the specimen of blood is taken. Widal and Lemierre[18] and Hohlweg[13] have shown, respectively, how the amount of protein ingested and how the length of time after a meal influences the incoagulable nitrogen content of the blood. Practically all of the cases studied by us have been on a low protein diet, containing from 50 to 75 gm. of protein, for varying periods of time, and although the blood was not obtained at any particular time of day, yet it was generally taken midway between meals.

According to Widal,[19] the urea of the blood as determined by the hypobromite method varies from 30 mg. to 50 mg. per 100 c.c., with the latter figure as the upper limit of normal. Widal and Ronchese[20] state that normally the nitrogen of this urea makes up 77 to 79 per cent. of the total incoagulable nitrogen. This, however, is not in accord with the findings when more accurate methods are used, and it appears quite certain that normally the urea nitrogen makes up about 50 per cent. of the total incoagulable nitrogen as noted by Schöndorff,[10] Strauss,[5] Obermayer and Popper,[12] Folin and Denis[16] and Oszacki.[17]

Since Folin and Denis[16] have shown so strikingly that there is constantly a greater amount of incoagulable nitrogen in the blood of hospital patents, even though they have no manifest signs or symptoms of renal insufficiency, and since Farr and Austin[7] obtained such varying results in persons with apparently normal kidneys, it becomes very difficult to fix a normal figure for the incoagulable nitrogen of hospital patients. From our series, however, we are inclined to believe that an incoagulable nitrogen content of 40 or even 50 mg. per 100 c.c. of blood, does not necessarily imply a clinical renal insufficiency.

PERSONAL OBSERVATIONS

The patients studied have been a portion of those entering the medical service of the university hospital complaining of symptoms pointing either to a renal or cardiac insufficiency, or to both, together with a few classed as miscellaneous. All the cases were first arranged in a series according to diminishing phthalein output, and this is indicated by the number. It was evident, however, that there was a fairly definite group which could be separated from the others, having a low phthalein excretion and at the same time a low incoagulable nitrogen. This group constitutes those given in Table 2, and will be discussed later.

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[18] Widal, F., and Lemierre, A.: Ergebn. d. inn. Med. u. kinderh., 1909, iv, 548.

[19] Widal, F.: Jour. Med français, 1911, v, 18.

[20] Widal and Ronchese: Compt. Rend. Soc. de Biol., 1906, lx, 245.

In Table 1 the observations are arranged in a series according to diminishing phthalein output. No relation between phthalein excretion and incoagulable nitrogen is evident until the phthalein output is definitely diminished. Patients 1 and 11 had nearly the same amount of incoagulable nitrogen, but in the former the phthalein excretion was 78 per cent. and in the latter 59 per cent. Cases 14 and 15, which clinically were very similar and in which the phthalein excretion was the same, differed markedly in the amount of incoagulable nitrogen.

Case 12, with a large amount of albumin in the urine, distinctly reduced chlorid excretion, normal phthalein elimination and normal incoagulable nitrogen, is of sufficient interest to report more in detail.

Case 12.—The patient, aged 17, had a negative family history and had had the usual diseases of childhood with uneventful recovery. At 10 a curvature of the spine was noticed which has been progressive; at 15 the patient noticed the ankles swelling and puffiness under the eyes. Albumin, edema and weakness have been constantly present since. At the time of admission the patient looked pale, had slight edema of eyelids and ankles and complained of being tired on exertion. There were no visual disturbances and no cardiac enlargement, and the systolic blood-pressure was 130. The red blood-cell count was 4,900,000, the white 10,500 and there was 86 per cent. hemoglobin. The daily output of urine varied from 500 to 900 c.c. on an intake of 1,200 c.c. of fluid, with a specific gravity ranging around 1.012 and an albumin content of 4 to 6 gm. per thousand. There were a few casts in the sediment. Potassium iodid in 0.5 gm. dose gave no test in the urine after fifty-six hours. On an ordinary diet the patient excreted sodium chlorid, 2 to 4 gm., in twenty-four hours. An addition of 10 gm. of salt to her diet was followed by an elimination of only 2.05 gm. with no increase in the specific gravity or amount of the urine and was accompanied by a slight gain in weight. As noted above, the phthalein elimination and incoagulable nitrogen of the blood were within normal limits.

Widal[19] has made a distinct type of this form of nephritis (*chlorurémie*), having a large amount of albumin, no increase of the incoagulable nitrogen of the blood, and a distinct impermeability of the kidney to chlorids, and several cases showing a normal phthalein elimination have been reported by Pepper and Austin[21] and by Baetjer.[22]

In our series of patients, when the phthalein output fell to 40 per cent. or less, there was an accompanying increase in the incoagulable nitrogen with certain notable exceptions, namely, in the cases from which Table 2 is made up, and in Case 21. This latter was a case of double pyelonephritis, due to colon bacillus infection, with low phthalein excretion and low incoagulable nitrogen. We have studied but one such case and are unable to say why so chronic and active a process should give rise to no accumulation of nitrogenous bodies in the blood. The cases making up Table 2 will be discussed later.

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[21] Pepper and Austin: Am. Jour. Med. Sc., Feb., 1913, p. 254.

[22] Baetjer, W. A.: Superpermeability in Nephritis, The Archives Int. Med., 1913, xi, 593.

Patient 27, who had chronic uremia, was under observation for some time, and shows very strikingly a falling phthalein excretion with an increasing amount of incoagulable nitrogen. Despite a further decrease in phthalein excretion, there was a sudden drop in the nitrogen content which remained practically constant. Three weeks elapsed between observations 27c and 27d, during which time the patient became edematous and hydremic. Edema and hydremia undoubtedly play an important rôle in the concentration of the incoagulable nitrogen, as has been noted by Hohlweg[13] and Strauss.[23] We would, therefore, explain this apparent discrepancy by assuming a condition of hydremia. The three cases in which there was no phthalein excreted showed a high incoagulable nitrogen, but it is seen that the two tests are not inversely proportional, since the highest incoagulable nitrogen was found in a case with about 10 per cent. phthalein excretion.

The relation of the urea-ammonia nitrogen to total incoagulable nitrogen varied greatly, from 23 per cent. in a patient with chronic parenchymatous nephritis to 96 per cent. in a patient with chronic uremia. In those patients who were uremic, however, the urea-ammonia nitrogen was in no case less than 71 per cent. of the total incoagulable nitrogen, but equally high percentages were obtained in several cases in which there was no nitrogen retention. Widal and Ronchese[20] have noted the increase of urea nitrogen over that of other nitrogenous substances in the blood of nephritics, but Foster[14] found that in uremia the urea nitrogen varied from 36 to 90 per cent. of the total incoagulable nitrogen, while similar observations have been made by Ascoli,[24] Obermayer and Popper,[12] Strauss,[15] and Folin and Denis.[16]

Since uremia has no definite symptom-complex, it should be stated at this point on what basis such a diagnosis has been made. We have taken the set of symptoms that Widal[18] has described as characteristic of *azotémie* or nitrogen retention, namely, great weakness and prostration, apathy, antipathy to food, muscular twitching, and a semistuporous condition. The clinical manifestations of uremia as we now know it are so varied that we regard it as very important to state definitely on what such a diagnosis is based. In none of our cases have there been marked gastro-intestinal symptoms or convulsions. Convulsions are probably not a part of pure nitrogen retention and ultimately we may be able to separate what we now rather loosely call uremia into several clinical entities. Strauss[15] has noted that there is no increase of the incoagulable nitrogen in uremia with convulsions.

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[23] Strauss, H.: Deutsch. Arch. f. klin. Med., 1912, cvi, 219.

[24] Ascoli: Arch. f. d. ges. Physiol., Pfluger's, 1901, lxxxvii 103.

TABLE 1.—Result of Tests in Twenty-Four Cases

No.	Name	Diagnosis	Phthalein Excretion	Incoagulable Nitrogen	Urea Ammonia Nitrogen	Urea	Percentage of Nitrogen as Urea	Hypebromite Nitrogen as Urea	Remarks
1	U.	Chronic nephritis; chronic hypertension.	78	0.021	0.011	0.023	52.8	0.044	Blood-pressure 200. Urine: trace albumin few casts.
2	R.	Chronic nephritis; acute thyroiditis and ethmoiditis.	77	0.012	0.008	0.017	67.5	0.031	Blood-pressure 185 to 235. Neuroretin Albumin and casts heavy.
3	O.	Chronic nephritis; chronic hypertension.	75	0.024	0.018	0.039	74.0	0.068	Blood-pressure 140 to 170. Trace albumin few casts. Neuroretinitis. Choked disk eye.
4	C.	Hypertension (temporary).	72	0.038	0.019	0.041	50.0	0.036	Blood-pressure 140 to 200. No albumin or c Neuroretinitis.
5	Car. ...	Chronic hypertension; cerebral arteriosclerosis.	71	0.017	0.012	0.026	70.7	0.047	Blood-pressure 200 to 235. No albumin, few c Fundus arteriosclerotic.
6	Jos. ...	Toxic psychosis.	68	.....	0.009	0.019	...	0.032	Died. Necropsy showed thrombophlebitis, lent bronchitis, emphysema, arterioscler chronic passive congestion, numerous hy glomeruli. No indican in blood.
8	Dunn. .	Chronic nephritis; arteriosclerosis; hypertension; myocardial insufficiency.	63	0.018	.....	.....	....	0.034	Blood-pressure 185 to 195. No albumin; casts.
9	H.	Chronic nephritis; chronic hypertension.	40	0.033	0.011	0.023	33.5	0.048	Phthalein for one hour only. Blood-pressure to 200. Distinct albumin and casts; no signs.
10	Ru. ...	Chronic hypertension; cystitis.	60	0.019	0.014	0.030	71.8	0.065	Blood-pressure 160 to 210. Trace albumin; casts.
11	F.	Fibroid of uterus; secondary anemia.	59	0.025	0.006	0.012	24.0	0.044	Blood-pressure 175. Urine negative. Reti each eye.
12	Ter. ...	Chronic parenchymatous nephritis; chlorid retention.	58	0.014	0.003	0.007	23.1	0.024	Large amounts of albumin. Marked chlorid tion. Two weeks later phthalein excretion 63.
13	Dra. ..	Syphilis; chronic nephritis; chronic hypertension; fibroid uterus; dilated aorta.	51	0.016	.....	.....	....	0.038	Blood-pressure 160 to 225. Large am albumin and casts. No marked fundus cha Living in same condition eight months lat
14	L.	Chronic nephritis; chronic hypertension.	49	0.058	0.043	0.092	74.2	0.059	Blood-pressure 200. Faint trace albumin few casts. Sudden death six months later
15	Rus. ..	Chronic interstitial nephritis; chronic hypertension.	49	0.019	0.008	0.019	44.5	0.075	Blood-pressure 155 to 190. Trace albumin an casts. Fundus arteriosclerotic.
17	We. ...	Pyelonephritis; myocardial insufficiency; mania.	39	.....	.....	.....	...	0.055	Blood-pressure 185. Albumin, casts and pu

May . . .	Chronic interstitial nephritis; uremia.	34	0.051	0.041	0.088	80.0	0.071	Blood-pressure 215 to 250. Much albumin an casts. Albuminuric retinitis. Some edema of eyes and limbs, cardiac hypertrophy, relative mitral.
T	Chronic interstitial nephritis; chronic uremia.	33	. . .	. . . . .	. . . . .	. . .	0.100	Blood-pressure 170 to 250. Much albumin an casts. Hemorrhagic retinitis. Observation below made one week later.
. . . . . .	. . . .	29	. . . .	. . . . .	. . . . .	. . . .	0.124	Died six weeks later in uremia.
Sean. . .	Pyelonephritis.	31	0.014	0.007	0.016	52.3	0.026	Blood-pressure 108. Trace albumin, few casts much pus. Working daily and in fair condition five months later.
J.	Chronic interstitial nephritis; chronic uremia; cardiac dilatation and hypertrophy; hydrothorax.	17	. . . . .	. . . . .	. . . . .	. . .	0.156	Blood-pressure 125 to 190. Heavy albumin an casts. Albuminuric retinitis. Died in uremi three months later.
. . . . . .	. . . .	13	0.128	0.117	0.250	90.8	0.256	Eleven weeks ante mortem.
. . . . . .	. . . .	. .	0.141	0.128	0.276	91.1	0.288	Ten weeks ante mortem.
. . . . . .	. . . .	10	0.060	0.048	0.104	80.0	0.138	Seven weeks ante mortem.
. . . . . .	. . . .	7	0.059	0.014	0.096	75.5	0.134	Three weeks ante mortem.
Murr. . .	Myocardial insufficiency; chronic interstitial nephritis; hypertension; arteriosclerosis.	12	0.067	0.037	0.080	55.7	0.155	Blood-pressure 210 to 225. Heavy albumin an casts. Edema. Died five days later. N necropsy.
Jock. . .	Chronic nephritis; uremia.	6	0.080	0.056	0.122	71.1	0.202	Blood-pressure 225 to 250. Urine: heavy albumi and casts. Albuminuric retinitis. Died i uremia six days later. No necropsy. Indica in blood positive.
. . . . . .	. . . .	.	. . . . .	. . . . .	. . . . .	. . . .	0.328	Twenty-four hours ante mortem. Six hours ant mortem spinal fluid gave 0.358.
G.	Chronic nephritis; uremia.	0	0.100	0.084	0.181	84.5	0.437	Blood-pressure 120. Urine: albumin and cast Indican in blood positive. Died in uremia thirt six hours later. No necropsy.
Mid. . . .	Chronic nephritis; chronic uremia; secondary anemia.	0	0.083	0.080	0.172	96.6	0.246	Blood-pressure 150 to 160. Urine: albumin an casts. Albuminuric retinitis.
M.	Uremia; anuria.	0	. . . .	. . . . .	. . . . .	. . .	0.474	Died six hours later. Necropsy showed hype nephroma of right kidney, chronic paren chymatous nephritis, chronic cystitis and py litis, chronic prostatitis with recent absces chronic vesiculitis, localized chronic meningiti Endocardium sclerosed also coronary and ren vessels, obliterative endarteritis, chronic pas sive congestion, atrophy of all organs. O syphilis (?).

As to the hypobromite method it is seen that its results varied greatly from those obtained by the Folin method. In general, the results by the latter are about 50 per cent. of those obtained by the hypobromite method, but when the nitrogen as urea made up a relatively larger part of the total incoagulable nitrogen the results by the Folin method approach those by the hypobromite method. In only three instances, in Cases 4, 14 and 18, were the results by the Folin higher than those by the hypobromite method. These variations may in part be due to an error in the hypobromite determinations, since only one analysis was made by this method, and also in the hypobromite determinations after precipitating with alcohol, as a second precipitation with zinc chlorid was not made. There is better agreement between the two methods when higher values are obtained and in spite of the wide variations we believe the hypobromite method to be a fair index of the urea content of the blood when there is a definite urea retention.

It is therefore evident that the hypobromite determinations must bear a rough relationship to the total incoagulable nitrogen. Table 1 shows that this relationship is not even so definite as that between the results obtained by the hypobromite method and the urea by the Folin method. This may be due to error in the hypobromite determinations or to its inherent faults, but with higher values the results are more in accord. Since the relationship between urea nitrogen and total incoagulable nitrogen is variable and since the hypobromite method is not an accurate method for urea determination, it is suitable as a guage of the incoagulable nitrogen of the blood only when there is a definite nitrogen retention, in which case the variables tend to disappear.

Table 2 is made up from those cases in which a diminished phthalein excretion was found with no increase of the incoagulable nitrogen of the blood. The symptoms of these patients without exception were those of cardiac insufficiency. In other words, these patients with cardiac insufficiency could eliminate nitrogenous products with ease but the kidneys showed a decreased permeability to phthalein. Hohlweg[13] found that cases of cardiac decompensation showed very little increase of the incoagulable nitrogen of the blood even when patients were moribund. Foster[14] found great variation in the incoagulable nitrogen of his uremic cases, but suggests that the cardiac element may be the explanation of the fatal issue in those cases having a low incoagulable nitrogen.

Rowntree, Fitz, and Geraghty[25] have shown experimentally that chronic passive congestion gives rise to a reduced phthalein excretion without marked increase of the incoagulable nitrogen. Rowntree and

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[25] Rowntree, Fitz and Geraghty: The Effects of Experimental Chronic Passive Congestion on Renal Function, The Archives Int. Med., 1913, xi, 121.

TABLE 2.—RESULT OF TESTS IN NINE CASES

Name	Diagnosis	Phthalein Excretion	Incoagulable Nitrogen	Urea Ammonia Nitrogen	Urea	Percentage of Nitrogen as Urea	Hypobromite Nitrogen as Urea	Remarks
Hep. . .	Cardiac insufficiency, dilatation and hypertrophy; chronic nephritis.	66	....	.....	.....	...	0.046	Blood-pressure 200, falling to 120. Distin albumin and casts. Much edema, chlorid rete tion. Retinal hemorrhages. Died seven montl later of cardiac insufficiency. No necropsy.
		48	0.040	0.018	0.038	45.0	. .	Five months ante mortem.
V.	Cardiac insufficiency; chronic nephritis; chronic gastritis.	42	0.015	.....	.....	....	0.038	Blood-pressure 155 to 170. Albumin and cas moderate. Retinal hemorrhages. Died tv months later of cerebral hemorrhage.
S.	Myocardial insufficiency; mitral stenosis; auricular fibrillation.	32	0.016	0.009	0.020	56.5	0.046	Blood-pressure 120. Urine contains albumin ar red blood-cells.
Up. . . .	Myocardial insufficiency; chronic nephritis; arteriosclerosis.	31	.....	....	...	....	0.037	Blood-pressure 175 to 200. Albumin and cas positive.
Gar. . .	Myocardial insufficiency; mitral regurgitation.	28	....	....	.	....	0.081	Blood-pressure 150. Much albumin, few red bloc cells, few casts. Much edema and chlor retention. Died one month later. Necrop showed cardiac dilatation and hypertroph mitral valves sclerotic.
Do.	Myocardial insufficiency; arteriosclerosis; chronic nephritis (?).	26	0.021	0.010	0.022	51.4	0.031	Blood-pressure 170. Trace albumin and cas Few fundus changes. Phthalein two weeks la was 36 per cent. In good condition five mont later.
W. . . .	Myocardial insufficiency; chronic nephritis; secondary anemia.	24	0.012	0.007	0.015	55.4	0.053	Blood-pressure 170 to 190. Trace albumin a casts. Albuminuric retinitis. Phthalein week later was 55 per cent. Indican in blo negative.
Mor. . .	Cardiac insufficiency; chronic nephritis; lobar pneumonia.	22	0.031	0.022	0.047	69.9	0.080	Blood-pressure 180 to 200. Albumin and ca moderate. Fundus sclerotic. Died twelve da later. No necropsy.
Y. . . .	Myocardial insufficiency.	..	....	.....	....	....	0.080	Blood-pressure 140 to 155. Urine heavy w albumin. Died thirty-six hours later. Necro showed cardiac thrombosis, syphilitic aort and myocarditis, chronic passive congesti chronic parenchymatous nephritis with multi infarcts, chronic prostatitis, cystitis, vesicul and pyelitis.

Fitz[26] found a low nitrogen content in their cases of pure cardiac insufficiency. Farr and Austin[27] had a similar experience and suggest that a low incoagulable nitrogen may serve as a means of separating cardiac cases. In our experience this has been true and by means of the incoagulable nitrogen of the blood we have been able to separate our cardiac cases from those with chiefly renal involvement.

From a diagnostic point of view the estimation of urea and the incoagulable nitrogen of the blood was found to be especially helpful in cases of coma and incipient "uremia"; in conjunction with the phthalein test it has enabled us to separate the cardiac cases.

As to prognosis all of the cases studied having an incoagulable nitrogen of 60 mg. or more per 100 c.c. of blood died within a period of weeks with symptoms of renal insufficiency, as did also all cases having a urea content of 100 mg. or more per 100 c.c. of blood by the hypobromite method. There was no relation between length of life and degree of nitrogen retention. Our experience as to the general significance of a high incoagulable nitrogen content is that of other observers and we believe it to be of great help in prognosis in those cases of nephritis in which there is a moderate reduction in phthalein elimination. A large percentage of our patients with cardiac insufficiency died and the estimation of the incoagulable nitrogen in these cases was not of the same value in prognosis as in diagnosis.

SUMMARY AND CONCLUSIONS

1. In general when the excretion of phenolsulphonephthalein was diminished below 40 per cent., there was a definite increase in the incoagulable nitrogen of the blood, except in one case of pyelonephritis and in those patients who were suffering chiefly from a cardiac decompensation.
2. The percentage of urea nitrogen to total incoagulable nitrogen varied widely but in cases of nitrogen retention it was uniformly high.
3. The hypobromite method gave high results which were inconstant but it served as a fair index of the urea content of the blood when there was definite nitrogen retention.

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[26] Rowntree and Fitz: Studies of Renal Function in Renal, Cardiorenal and Cardiac Disease, The Archives Int. Med., 1913, xi, 258.

[27] Farr and Austin: Jour. Exper. Med., 1913, xviii, 228.

A COMPARISON OF METHODS OF OBTAINING ALVEOLAR AIR *

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The recent advances in our knowledge of the physiology of respiration and of the mechanism by which the normal reaction of the blood is maintained have opened wide fields for study in clinical medicine. In many of the problems which present themselves it is essential to have information regarding the tension of gases in the alveolae of the lungs. While it is comparatively simple to obtain satisfactory samples of alveolar air from trained workers, it is a much more difficult task when dealing with the average hospital patient, for unfortunately all the methods yet devised depend in part on the cooperation of the subject himself. Lack of intelligence, lack of interest, pain, dyspnea, restlessness, toxemia, unconsciousness and the natural disinclination of the sick person to take part in any active performance are among the many factors which interfere with the taking of reliable samples of alveolar air. Preliminary, therefore, to the study of alveolar air in pathological conditions, we have considered it necessary to make a comparative study of the various methods of obtaining alveolar air in order to determine the advantages and disadvantages of each method, the conditions under which a given method is best applicable, and in general to decide on which methods are most reliable for the study of clinical cases. The present report is based on approximately five hundred observations, on hospital patients, as well as on laboratory workers, most of whom were untrained in the methods of taking alveolar air.

THE HALDANE METHOD

The method as devised by Haldane[1] consists in the use of a ¾-inch hose about 4 feet long fitted with a glass mouthpiece at one end. The subject, after five minutes' normal breathing, gives the greatest possible expiration through the tube. This should be done rapidly to ensure the displacement of the air in the hose. At the end of the expiration the subject closes the mouthpiece with his tongue, and the sample of air is drawn from the beginning of the tube. Two samples should be taken—

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* From the Surgical and Medical Services of the Peter Bent Brigham Hospital.

[1] Haldane and Priestley: Jour. Physiol., 1905, xxxii, 225.

one from an expiration beginning at the end of normal inspiration, the other from an expiration beginning at the end of normal expiration. The values of the two samples are averaged.

This method is without doubt the best and simplest for the trained subject. For an untrained person, and especially for one of moderate intelligence, the use of the tongue in closing the mouthpiece presents an almost insurmountable difficulty. To overcome this we have modified the technic by introducing a specially constructed valve.

THE HALDANE METHOD WITH A SPECIALLY DESIGNED VALVE

The general objection to the use of a valve is that currents and eddies of air are formed which probably introduce a real element of uncertainty. While this is certainly true of the ordinary valve, we believe that the one to be described effectually overcomes this difficulty, and greatly increases the usefulness of the Haldane method.

The valve is a hollow copper cylinder about 4 inches in diameter and 1 inch long, closed at both ends. Set into each end of the cylinder, and opposite each other, are two brass tubes of ¾-inch diameter. Inside the main cylinder is another cylinder, ground so as to fit accurately, which revolves through an arc of about 45 degrees. The inside cylinder is pierced by two ¾-inch tubes, one of which is open at both ends, and so placed that when set opposite the two tubes previously mentioned a mouthpiece and straight tube about 4 inches long is formed. The far end of the tube is attached to a rubber hose 4 feet long, as in the ordinary Haldane alveolar air-tube. A single, almost instantaneous movement by means of a handle throws the second tube of the inner cylinder into communication with the mouthpiece. This tube is open at the side and closed at the far end, an arrangement which allows the subject to breathe naturally through the mouthpiece to the outside air with a dead space of not over 20 cm.

The apparatus is used as follows: The subject breathes naturally for five minutes through the mouthpiece directly to the outside air. At a given signal, at the end either of inspiration or of expiration, the observer turns the handle quickly and puts the subject into communication with a 4-foot tube that is perfectly straight and smooth. At the same instant the subject expires as deeply and rapidly as possible, and at the very end of the expiration the observer turns the handle back. The subject now breathes to the outside air and the alveolar air is sealed in the rubber tube. The sample is then quickly drawn into the sampling-pipet.

This method has proved itself to be of great value and we invariably use the valve when we are taking alveolar air by the Haldane method.

The relative accuracy of the Haldane method with and without the valve is shown by the following observation:

April 9, 9 a. m.; B.: With valve: Inspiration, $CO_2 = 41.1$ mm.; expiration, $CO_2 = 41.3$ mm. Without valve: Inspiration, $CO_2 = 39.9$ mm.; expiration, $CO_2 = 40.1$ mm.

The Haldane method in one of its various modifications should be classed as the standard method of taking samples of alveolar air since it undoubtedly gives the most accurate values when used under proper conditions. Its clinical applicability is limited to patients who are in comparatively good health. To obtain satisfactory samples it is necessary not only that the expiration should be as complete as possible, but also that it be rapid and forcible. A slow prolonged expiration is not sufficient. Many sick patients are unable, on account of pain or dyspnea or weakness, to give an expiration of enough force and depth. In these and in patients of distinctly low intelligence the method is unreliable. We have found, moreover, that even among intelligent, healthy persons it frequently takes considerable training before satisfactory results are obtained.

THE LINDHARD METHOD

Lindhard[2] has recently described the following very ingenious way of obtaining alveolar air: The subject breathes through a Krogh glass valve with rubber flaps and dead space of from about 40 to 50 c.c. Through an opening directly opposite the mouth is passed a small flexible lead tube with an interior bore of about 1 mm. This lead tube passes back into the pharynx so far as possible for comfort. The samples of air are drawn with a sampling-tube in 3 or 4 c.c. amounts at the end of a normal expiration. Accordingly to Krogh and Lindhard, this is reliable in subjects breathing 600 c.c. or over per respiration. The essential point in this method is the exact time at which the samples are taken, and this is somewhat difficult for the observer. If taken either just too early or too late alveolar air is not obtained. The movement of the rubber valve-flaps is an aid in timing.

We have made an extensive trial of this method and have found it to check up with the Haldane method if the subject breathed deeply. In the ordinary person 300 or 400 c.c. is the normal expired air; therefore, we were obliged to have the subject exhale about double his usual amount on a given signal; we repeated these deep exhalations about every forty-five seconds.

In order to determine more accurately the influence of the depth of expiration on this method of taking alveolar air, the valves were attached to a recording spirometer, and the volume measured of those expirations, at the end of which the samples were taken.

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[2] Linhard: Jour. Physiol., 1911, xlii, 337.

March 10, 3:30 p. m.; P.: Volume of expiration $= 399$ c.c.; alveolar $CO_2 = 29.9$ mm. Volume of expiration $= 440$ c.c.; alveolar $CO_2 = 34.5$ mm.

Control by two Haldane samples (valve) $= 41.3$ mm. and 38.9 mm.; 40.1 mm.

It is thus evident that samples taken at the end of normal expirations are not alveolar air. The percentage of carbon dioxid is much lower than it should be. The following experiments show the results which may be obtained when samples are taken at the end of deeper expirations:

April 3; P.: Volume of expiration $= 880$ c.c.; alveolar $CO_2 = 40.2$ mm.
Volume of expiration $= 1{,}200$ c.c.; alveolar $CO_2 = 39.5$ mm.
Volume of expiration $= 1{,}650$ c.c.; alveolar $CO_2 = 36.5$ mm.
Volume of expiration $= 870$ c.c.; alveolar $CO_2 = 36.5$ mm.
Volume of expiration $= 1{,}000$ c.c.; alveolar $CO_2 = 38.8$ mm.
Volume of expiration $= 1{,}250$ c.c.; alveolar $CO_2 = 40.1$ mm.
Control by two Haldane samples (valve); inspiration, $CO_2 = 41.1$ mm.
expiration, $CO_2 = 41.6$ mm.

April 4; P.: Volume of expiration $= 650$ c.c.; alveolar $CO_2 = 38.0$ mm.
Volume of expiration $= 670$ c.c.; alveolar $CO_2 = 35.3$ mm.
Volume of expiration $= 840$ c.c.; alveolar $CO_2 = 37.8$ mm.
Volume of expiration $= 690$ c.c.; alveolar $CO_2 = 37.6$ mm.
Volume of expiration $= 840$ c.c.; alveolar $CO_2 = 39.6$ mm.
Volume of expiration $= 1{,}460$ c.c.; alveolar $CO_2 = 39.4$ mm.
Volume of expiration $= 880$ c.c.; alveolar $CO_2 = 39.2$ mm.
Volume of expiration $= 540$ c.c.; alveolar $CO_2 = 38.2$ mm.
Volume of expiration $= 800$ c.c.; alveolar $CO_2 = 38.3$ mm.
Volume of expiration $= 1{,}500$ c.c.; alveolar $CO_2 = 39.2$ mm.
Control by two Haldane samples (valve); $CO_2 = 38.5$ mm.
$CO_2 = 38.5$ mm.

Inasmuch as these were the results obtained in a series of consecutive experiments with a subject who was not particularly well trained, it will be noted that they are in close accord with the results by the Haldane method. In the instances in which the carbon dioxid is low, beyond the limit of error, the timing of taking the samples was undoubtedly at fault. It is thus quite possible to obtain accurate samples of alveolar air by the Lindhard method even with persons whose respiration is normally shallow, if they are made to give occasional moderately deep expirations, and if a series of small samples are taken at exactly the end of such expirations.

Early in our studies we became impressed with the fact that untrained persons, and especially sick persons, were greatly inconvenienced by the use of valves. Indeed, the use of a simple mouthpiece may quite change the type of respiration, making it deeper than normal and more labored. This is especially the case with patients having a tendency to dyspnea. We therefore attempted to develop a method for obtaining alveolar air with as little as possible of the disturbing apparatus. The result is a modification of the Lindhard method.

THE LEAD TUBE METHOD

The subject breathes through his mouth, the nose as usual being closed by a nose-clip. A small flexible lead tube of 1 mm. bore is introduced into the mouth, and the end passed as far back as is possible without bothering the patient. At a point about 3 cm. from the mouth a small feather is attached to the tube to serve as an index of the phases of respiration. The other end of the lead tube is attached to one of the sampling-pipets used by Krogh, with an easy working tap at the top, but none at the bottom. The opening at the bottom of the tube must be wide so that the mercury falls rapidly and the sample is taken quickly. The subject breathes naturally and at a word given at the end of an inspiration gives a deep forcible expiration of at least 600 or 800 c.c. At almost the end of the expiration the tap on the sampling-tube is turned quickly and from 3 to 5 c.c. of air taken into the tube from the back of the mouth. Deep expirations are given at intervals until a large enough sample is obtained for analysis. The following examples illustrate the probable accuracy of the method:

April 13; Miss B.: CO_2 in successive samples A. (1) 38.8 mm.: (2) 40.9 mm.: (3) 39.1 mm.: (4) 38.8 mm. B. (1) 40.8 mm.; (2) 42.0 mm.; (3) 43.1 mm.:

Controls by Haldane method: Inspiration, $CO_2 = 41.8$ mm.
Expiration, $CO_2 = 41.9$ mm.

These figures present some interesting points for study. It is probable that the tension of carbon dioxid in the alveolar air of this patient was practically 42 mm. Series A was taken by one of us and Series B by the other. We have frequently seen a slightly lower average by one observer than by the other. We attribute this to the difficulty of exactly timing the opening of the tap, and do not consider that it represents an actual change in the alveolar air. The following experiments were done by the same method:

April 14; F.: CO_2 in successive samples = (1) 40.4 mm. (2) 41.3 mm.; (3) 41.3 mm.; (4) 40.5 mm. Average = 40.8 mm.

Controls by Haldane method: Inspiration, $CO_2 = 39.1$ mm. Expiration, $CO_2 = 41.3$ mm. Average = 40.2 mm.

April 15; B.: CO_2 in successive samples = (1) 38.2 mm.; (2) 40.0 mm.; (3) 39.2 mm.; (4) 38.2 mm. Average = 38.9 mm.

Controls by Haldane method: Inspiration, $CO_2 = 37.2$ mm. Expiration, $CO_2 = 41.5$ mm. Average = 39.3 mm.

April 16; B.; CO_2 in successive samples = (1) 38.6 mm.; (2) 39.8 mm.; (3) 40.0 mm.; (4) 40.1 mm. Average = 39.6 mm.

Controls by Haldane method: Inspiration, $CO_2 = 38.9$ mm. Expiration, $CO_2 = 41.0$ mm. Average = 39.9 mm.

April 16; F.: CO_2 in successive samples = (1) 41.3 mm.; (2) 42.6 mm.; (3) 42.6 mm.; (4) 42.8 mm. Average = 42.1 mm.

Controls by Haldane method: Inspiration, $CO_2 = 40.0$ mm. Expiration, $CO_2 = 42.9$ mm. Average = 41.7 mm.

May 27; W. (patient): CO_2 in successive samples = (1) 42.4 mm.; (2) 43.0 mm. Average = 42.7 mm.

Controls by Haldane method: Inspiration, $CO_2 = 43.0$ mm. Expiration, $CO_2 = 41.4$ mm. Average = 42.2 mm.

June 2; S. (patient): CO_2 in successive samples = (1) 33.6 mm.; (2) 36.6 mm.; (3) 35.5 mm.; (4) 36.6 mm. Average = 35.6 mm.

Controls by Haldane method: Inspiration, $CO_2 = 35.3$ mm. Expiration, $CO_2 = 34.9$ mm. Average = 35.2 mm.

The chief disadvantage of the method is the difficulty of taking samples at exactly the right time. If they are taken too early or too late, the carbon dioxid values fall too low. It is thus advisable to take several tubes. Occasionally one analysis falls so far below the others that it is obviously incorrect and it must be discarded. The advantages of the method lie first in the fact that the valves or mouthpiece which upset the subject's natural respiration are discarded. Troublesome accumulation of saliva is avoided, as the tube can be removed from the mouth at any moment, and the subject allowed to swallow. Secondly, it is possible to obtain samples of alveolar air with less deep and forcible expirations than by the Haldane method because a number of small samples are taken from a series of expirations, rather than one large sample from a single expiration. In clinical work the method has proved to be of especial value with toxic or unconscious patients, in whom the alveolar ventilation is great. It is impossible to make these patients breathe as one desires, and their respiration is often changed when they are forced to breathe through a mouthpiece. Moreover, it is sometimes difficult to prevent leakage round a mouthpiece. The small lead tube can be passed into the mouth almost without the patients being aware of its presence, and the samples are taken at the end of expiration. The following analyses show the results obtained in a case of severe diabetic coma:

Oct. 2; B.: CO_2 in successive samples = (1) 6.2 mm.; (2) 6.2 mm.; (3) 5.5 mm.

Control by Plesch-Higgins method: $CO_2 = 6.7$ mm.

Oct. 3; B.: CO_2 in successive samples = (1) 11.0 mm.; (2) 10.8 mm.

Controls by Plesch-Higgins method: CO_2 = (1) 10.8 mm.; (2) 10.5 mm.

THE PLESCH METHOD

The principle of this method of determining the carbon dioxid tension of the alveolar air is quite different from that of the methods described above. Instead of attempting to obtain actual samples of air from the alveoli by means of deep expirations, Plesch[3] has suggested the rebreathing of a limited volume of air until it is in equilibrium with the air in the alveoli. Porges[4] and his associates have found this method satisfactory in series of clinical investigations. Porges states that the carbon dioxid diffuses so rapidly that an equilibrium is established before a single complete circulation of the blood has taken place. The apparatus, as we have used it, is the same in principle, and differs only in details of construction from that of Porges. The form was devised by Mr. H. L. Higgins, of the Carnegie Nutrition Laboratory, Boston. To a copper disk of about 20 cm. is soldered on the under side a flange 2 cm. wide. In the center of the same (under) side of the disk is soldered an ordinary ¾-inch three-way brass valve. Near this is soldered a small brass tap suitable for the attachment of small rubber tubing for taking samples of air. Over the top of the disk is stretched a woman's rubber bathing-cap, held in place on the flange by a large rubber band. The subject, with his nose clamped, breathes through a mouthpiece which is attached by a short piece of wide-bore rubber tubing to the three-way tap in the bottom of the copper disk. The tap is at first turned so that the subject breathes to the outer air. It is then turned so that the subject breathes in and out of the bag for a given length of time. The tap is then turned again, the bag is closed and a sample of air taken from the bag for analysis. Porges begins with the bag empty, lets the subject take a deep inspiration, and at the height of the inspiration turns the tap so that the subject expires into the bag and then rebreathes. Experiments with this technic, however, show that the tension of the carbon dioxid in the bag varies considerably with the depth of the initial inspiration, and thus with the amount of air in the system of respiratory tract plus bag. In the following the time and number of respirations were constant:

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[3] Plesch: Ztschr. f. exper. Pathol. u. Therap., 1909, iii, 380.

[4] Porges, Leimdorfer and Markovi: Ztschr. f. Klin. Med., lxxiii.

March 13; B.: Moderately deep initial inspiration: $CO_2 = 43.2$ mm.
Deeper initial inspiration: $CO_2 = 41.5$ mm.
Very deep initial inspiration: $CO_2 = 38.2$ mm.
Controls by Haldane method: Inspiration, $CO_2 = 41.2$ mm.
Expiration, $CO_2 = 41.2$ mm.

This source of error is to some degree at least avoided if one follows the suggestion of Higgins and fills the bag with a constant volume of air. The tap is then turned at the end of a normal expiration, and the patient begins by inspiring from the bag. This is the method which we have adopted, but instead of filling the bag with 600 c.c. of air (Higgins) we find it more satisfactory to fill with 1,000 c.c. of air, and thus allow the subject to take a deeper inspiration. The air is forced into the rubber bag through the small tap by water displacement from an ordinary flask.

The time during which breathing takes place is of considerable importance. Porges[4] states that after from twenty to thirty seconds there is very little change in the composition of the air. His experiments, however, show that practically there may be a considerable rise in the carbon dioxid tension if the same air is rebreathed for twenty-five-second periods after various intervals. We have performed a similar experiment and have found that after breathing from the bag four times in twenty seconds the carbon dioxid tension of the air in the bag was 39.5 mm. After an interval of three and one-half minutes the same air was rebreathed for two periods of twenty seconds each, the periods separated by an interval of one minute. The carbon dioxid tension in the bag was then 45.9 mm. After rebreathing for two more similar periods the carbon dioxid tension had risen to 46.4 mm. There may also be a rise in the carbon dioxid tension if the length of the single periods is prolonged. Thus successive determinations with the same patient gave the following results:

Four respirations in 20 seconds: $CO_2 = 45.2$ mm.
Six respirations in 30 seconds: $CO_2 = 47.4$ mm.
Eight respirations in 40 seconds: $CO_2 = 48.6$ mm.

The element of time is therefore an important one, and we have found, in agreement to Porges, that from twenty to thirty seconds, and preferably twenty-five seconds, is the optimum.

The question of the rate and depth of respiration while rebreathing is of some moment. Within certain limits, however, they seem to play a lesser rôle than one might anticipate. The following successive determinations were made on the same person (P.) the rate and depth of the respirations being varied:

Five	respirations in 25 seconds.	Moderately deep	$CO_2 = 46.4$ mm.
Sixteen	respirations in 25 seconds.	Shallow	$CO_2 = 45.9$ mm.
Five	respirations in 25 seconds.	Very deep	$CO_2 = 46.3$ mm.
Seventeen	respirations in 25 seconds.	Shallow	$CO_2 = 45.4$ mm.
Five	respirations in 25 seconds.	Natural	$CO_2 = 39.0$ mm.
Five	respirations in 25 seconds.	Moderately deep	$CO_2 = 45.1$ mm.

Thus with the exception of the fifth determination, in which the subject was breathing naturally, quietly and superficially, the values of the carbon dioxid tension agreed well, whether the respirations were very deep or were shallow and rapid. Gentle, superficial respiration does not suffice to bring about complete diffusion of gases. The same has been found to be true of very rapid, superficial, panting breathing, which also gives too low values for the carbon dioxid tension. Respirations of moderate depth, however, seem to bring about as complete diffusion as very deep respirations. The results of a large number of determinations lead us to agree with Porges in feeling that the best results are obtained if five rather deep respirations are taken in the twenty-five seconds.

In regard to the accuracy and reliability of this method of taking alveolar air, one must first consider the constancy of the results obtained by the method and then the relation of the results obtained to those found by other methods. A comparatively large number of observations have now been made on patients and more or less experienced laboratory workers. The results depend, of course, in some degree on the experience of the subjects and on their intelligence in understanding what is required of them. In general, however, it has been striking that reliable observations have been obtained with comparative ease from almost all hospital patients. At least two experiments are made for each determination. The results very frequently agree within 1 mm. tension of carbon dioxid. Almost always they agree within about 2 mm. tension. While this is perhaps not the highest degree of accuracy, it must be remembered that it is extremely difficult to achieve greater accuracy in obtaining samples of alveolar air by any method except in trained subjects, so that on the whole the results are satisfactory as far as their constancy is concerned. A series of observations has also been made comparing those obtained by the Plesch method with those obtained by the Haldane method in the same subject and at the same time. The relation is, of course, a variable one, but the Plesch method almost always gives a higher value for carbon dioxid tension. On the average it is approximately from 1 to 4 mm. higher, but sometimes it is less and sometimes a little more.

The advantages in the use of the Plesch method are obvious. From the point of view of the subject it is extremely simple, and satisfactory results can be obtained from almost any one with a minimum of training. It is frequently extremely difficult to make a sick person or, in fact, many healthy persons, give an expiration of maximum depth, but almost any one can easily breathe deep enough to give reliable results by the Plesch method. Moreover, the technic required of the observer is so simplified that it is readily acquired and needs very little skill. The chief disadvantage of the Plesch method is that it is not quite so accurate as the Haldane method. This, however, seems to be only with regard to highly trained subjects. In a person of experience and intelligence it is possible to obtain constant and accurate results by the Haldane method, but in the average run of persons the results obtained by the Plesch method are on the whole more satisfactory. The Plesch method is worked out on a more empirical basis, but it gives very constant values, and values which are extremely satisfactory for comparative studies.

SUMMARY

As a result of an extensive comparative study of various methods for obtaining the tension of gases in the alveolar air, with especial reference to the use of these methods in clinical work, we have arrived at the following conclusion:

The Haldane method gives results which approximate closely the average gaseous composition of the alveolar air. It is the most reliable and accurate method when used on intelligent and experienced subjects. The necessity, however, of obtaining very deep and very forcible expirations limits its usefulness when working with untrained or sick persons.

The Lindhard method, and the modification of it described here, give values analogous to those of the Haldane method. The method has the advantage, however, of not requiring such deep expirations as the Haldane method. The technic of taking the samples is, however, much more difficult for the observer. In certain types of pathological cases, notably in unconscious or very sick patients with a large alveolar ventilation, the method is useful and the technic simple.

The Plesch method gives values for the carbon dioxid tension which are higher than those obtained by the Haldane and Lindhard methods. Successive determinations give sufficiently constant values. The technic of the method both for the observer and for the subject is so simple that the method is especially useful for routine clinical work.

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BOOK REVIEW

Organic and Functional Diseases. A Text-Book of Neurology. By M. Allen Starr, M.D., Ph.D., LL.D., Sc.D., Professor of Neurology, College of Physicians and Surgeons, New York. Fourth edition, enlarged and thoroughly revised. Octavo, 970 pages, with 323 engravings and thirty plates in colors or monochrome. Cloth, $6.00, net. Lea & Febiger, Philadelphia and New York, 1913.

The fact that a text-book has reached a fourth edition is unmistakable evidence of its popularity, but when the subject is one undergoing rapid change there is always danger of unevenness of treatment and overlooking important details. Dr. Starr's book has been justly noted for its clear manner of presentation, the fulness and accuracy of the clinical and anatomical descriptions and the judicious methods of treatment advised. In the present edition the good qualities are retained and in many details the work is brought well up to date. At the same time the reviewer can find some things that a more thorough revision might have changed for the better. The first chapter, for example, on the method of examination, is so sketchy as to be useless to a beginner—say an undergradute working in a clinic — and too conventional to be of value to the practitioner who wishes to refresh his knowledge of such matters. The anatomic account deserves similar criticism. Nevertheless, both methods of examination and anatomic details are considered in the course of the work, so that the criticism bears more on composition than on any lack of information. The latter is usually available and is always interesting as well as sound, as in the remarks on Freudian views and methods. As an evidence of the completeness of review we may cite the account of the changes in spinal fluid — so essential in diagnosis — and the chapter on poliomyelitis. Still, as a result of the rapid advance of knowledge, although the book includes references to work done in the early part of 1912, the discovery of the germ of poliomyelitis came too late to be included. As an evidence of unevenness the section on beriberi may be mentioned. In this practically no reference is made to the important researches on nutritional factors and the interesting subject of the vitamines. One wishes also that the author had discussed more fully the relation of pernicious anemia to spinal cord changes. The references to the Calmette test in the diagnosis of tuberculous infections and the finding of tubercle bacilli in the spinal fluid in meningitis are certainly based on insufficient consideration of the facts. On the other hand, all through the work one cannot but be impressed with the extent of the author's clinical experience and his familiarity with the literature, and their analysis up to the time of publication. The sections on treatment are usually full, judicious and well founded. It is all the more surprising then to find Warburg's tincture so highly praised for malarial affections, for that mixture has probably been most successful, outside of India, in the treatment of diseases in which the diagnosis of malaria has been anything but accurate. The aphoristic definition of parasyphilitic lesions as caused by syphilis, but not curable by antisyphilitic treatment is, perhaps, unduly pessimistic by reason of our rudimentary knowledge of methods of treatment. The important investigations of Noguchi and Swift suggest a better prospect. Perhaps it would be wrong to criticize the author for speaking of alcohol as a heart stimulant, but the direction for giving nitroglycerin hypodermically in whisky or brandy shows a curious ignorance of the absorption of nitroglycerin. One must be grateful to the author for his candid condemnation of goat-lymph, so-called, so much abused by charlatans.

On the whole, the good points in the book so far outweigh the faults that the work is sure to prove in its present form a valuable aid and guide in the spread of neurologic information. It is unfortunate that it had to be printed on such heavy paper. Any gain that was intended for the illustrations was lost, for the latter vary much in quality and those for which the paper was perhaps chosen are not nearly as good as others.

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SYSTEMIC BLASTOMYCOSIS

A REPORT OF ITS PATHOLOGICAL, BACTERIOLOGICAL AND CLINICAL FEATURES *

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CHICAGO

The object of this report is so to relate the observations made in connection with a number of cases of systemic blastomycosis that a better understanding may obtain of the disease not only in this locality, where clinicians are already quite familiar with it, but also in places where it has been encountered but rarely or not at all.

Two summaries of the literature have already been made, that by Hektoen[1] dealing with thirteen cases, and the one by Montgomery and Ormsby[2] with twenty-two.

The second of these reviews contains brief accounts of the illnesses of four patients in this series and the post-mortem examinations on the bodies of two of them. The other two patients have since died and we are able to add the more detailed clinical records and the final results of the studies of material from two additional post-mortem examinations.

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* Under the title "Medical and Surgical Reports of the Cook County Hospital for the Six Months Ending July 1, 1890," the first report containing scientific articles from this institution was published; it was edited by Louis J. Mitchell, M.D. A second report also edited by Dr. Mitchell with a similar title covered the succeeding six months. The third scientific report was entitled "Cook County Hospital Reports, 1906." It was compiled and edited by a committee of the attending staff and contained material which for the most part had been published elsewhere. The fourth and last report of this character was published in 1910. Like the third it bore the title "Cook County Hospital Reports." It was edited by a committee with Dr. E. R. LeCount as chairman. None of the articles in it had or have since been published elsewhere. Fifteen hundred copies of this report were printed bound in black cloth. Only three are at present known to be in existence. The remainder disappeared about the time there was a change in the board of commissioners of Cook County as well as a considerable change in the political composition of this board. What became of these reports is not definitely known. According to rumors they were burned by mistake. It has been thought best to reproduce the articles on blastomycosis which occupy 160 of the 196 pages in the original volume, since the observations they contain regarding this relatively rare disease would otherwise be lost or escape notice entirely.

[1] Hektoen, Ludwig: Systemic Blastomycosis and Coccidioidal Granuloma, Jour. Am. Med. Assn., 1907, xlix, 1071; Chiari's Festschrift.

[2] Montgomery, F. H., and Ormsby, O. S.: Systemic Blastomycosis, The Archives Int. Med., 1908, ii, 1.

On account of the involvement of the bones, Dr. E. W. Ryerson[3] has considered the clinical and pathological relations of such changes to diseases for which it might be mistaken and utilized the observations made in connection with two cases of this series. To these five cases which have been but partially reported, there are added the hitherto unpublished observations on six additional cases, making the total number reported twenty-nine. I know of seven other instances of systemic blastomycosis, some of which will undoubtedly be published in the near future; six of these concern patients in Chicago or the immediately surrounding country. Of the twenty-nine cases reported, fourteen have concerned patients in Cook County Hospital, and of these eleven have occurred in the last two years. The total, thirty-six, represents an increase of over 200 per cent. during the last two years, and this without doubt is due to the great familiarity of physicians, especially the better clinicians, with the manifestations of the disease.

There are good reasons, as others have pointed out, for believing that the disease is frequently mistaken for tuberculosis; and judging from a number of the clinical histories in this series, it is evident that such errors are still likely to occur even here where the condition is perhaps best known.

The disease seems to be one of early life, as two-thirds of the patients have been under the age of 34, the youngest 17, the oldest 58 years of age; all but two occurred in men. The occupation in nearly every instance was one involving hard manual labor and considerable exposure. Heredity seems to have no influence, and no definite instance of contagion has been established. When this seems to have occurred, the exposure of all affected to a common case must be remembered. The majority of the patients have been foreigners, especially Poles and Italians, but no special nativity predilection has been noticed. Nearly all were poor and lived in unhygienic environment. Injury seems to have been a predisposing factor in several instances, either by affording opportunity for direct inoculation (see Cases 3 and 12 in the accompanying bibliography) or producing a region of lowered resistance for the development of the infection already existent (Cases 8 and 23).

The cause of this disease is now generally recognized to be a mold which, because of the budding form of the organism in the tissues, has been called blastomyces.

The reasons for considering the blastomyces as the cause of blastomycosis are, briefly, its presence in all the new or recent lesions, the readiness with which it is obtained from such lesions in pure culture, and the experiments on animals which demonstrate its pathogenicity. The organism has been recovered from the blood and is present in the pus of unopened and discharging abscesses, quite regularly present in the sputum and sometimes demonstrated in the urine or feces.

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[3] Ryerson, E. W.: Am. Jour. Orthop. Surg., 1908, vi, No. 1.

Numerous descriptions of the organism, its cultural peculiarities and variations in morphology have been published.[4]

Some confusion still exists regarding the classification of blastomycetes and especially in regard to the significance of variations observed during the cultivation of different strains. Differences were first noticed in the study of organisms obtained from the cutaneous lesions of blastomycotic dermatitis, and Ricketts, in comparing the characteristics of seventeen organisms, six under his personal observation, found variations in their manner of growth sufficiently constant and distinct to allow of a classification into three morphological types, namely, blastomycetoid, oidium-like and hyphomycetoid.

The identity of the organism causing these cutaneous lesions and those found in the systemic infections was at first questioned, but as cases of the latter became more numerous, their identity was generally recognized. It was then ascertained that the variations were not sufficiently constant to allow of a separation into distinct types. Hamburger,[4] in a recent comparative study of four strains of blastomycetes obtained from patients with systemic infection, found one which differed somewhat from the other three, but not sufficiently to prevent the conclusion that the organisms were identical. Still more recently Montgomery and Ormsby have asserted that all the morphological types hitherto described have been observed at different times in the same strain. Many of the studies dealing with these matters have extended over rather limited periods of time and included comparatively few strains. We have studied altogether eleven strains: eight from the cases here reported (Cases 19 to 26) and three others, to the source of which reference will be made. The observations extended over a period varying in the individual strains from two to twenty months. In all instances the organisms were obtained in pure culture from the pus aspirated from abscesses, and similar organisms were also obtained in cultures from the sputum in most cases. They were also obtained from the blood of one patient (Case 19) and from the eye, pericardium and pleura in another (Case 20). A number of different cultures as to source were therefore obtained from each patient; and as they possessed no differences (except in Case 19) only one or two from each patient were used in the comparative study.[5]

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[4] Ricketts, H. T.: Jour. Med. Research, 1901, vi, No. 3; Montgomery, F. H.: A Brief Summary of the Clinical, Pathologic and Bacteriologic Features of Cutaneous Blastomycosis (Blastomycetic Dermatitis of Gilchrist), Jour. Am. Med. Assn., 1902, xxxviii, 1487; Hamburger, W. M., Jour. Infect. Dis., 1907, iv, 201.

[5] The organisms will be designated according to the case from which they were obtained.

As may be presumed, the morphological and cultural details of these different strains of organisms presented marked similarities, and in order to prevent repetition of details one general description will be given with the variations noted.

The organisms in the tissues, discharges and pus corresponded with those described in previous reports. They appeared in pairs or clumps as round or oval bodies, and budding was a common feature (Fig. 1).[6] The size usually varied, those about 20 microns in diameter being the most frequent, although larger forms (from 25 to 30 microns) were not uncommon, and innumerable smaller forms (from 3 to 5 microns) were sometimes found. Ordinarily the outer refractile capsule and clear central portions could be recognized. The capsule was homogeneous and double-contoured, and varied in thickness, being thinner in the smaller and younger forms. It was occasionally absent, especially in the organ-

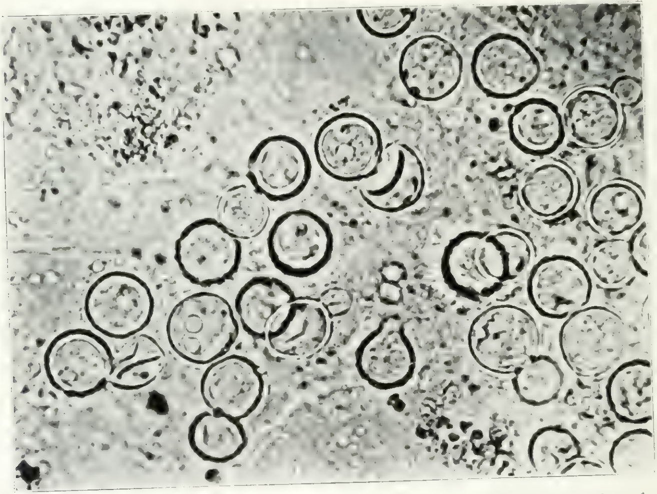

Fig. 1.—Specimens of pus containing blastomycetes mounted in a solution of potassium hydroxid. Note the round and budding forms, the refractile capsule and the vacuoles and granules in the center. (Courtesy of Dr. O. S. Ormsby.)

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[6] The illustrations presented in this and the following articles on blastomycosis were (except where noted) prepared by me and formed the basis of a research exhibit presented at the 1908 session of the American Medical Association. The roentgenograms were prepared by Dr. H. E. Potter, roentgenographer to the Cook County Hospital, and are included in an article on "Radiographic Appearances of Pulmonary and Osseous Blastomycosis," published in the American Quarterly of Roentgenology, May, 1910.

isms of old foci. In sections of a bone-abscess a thick or adventitious capsule described by other writers was found. The capsule rarely stained by the ordinary methods. The central portion in the fresh condition was usually clear, and stained more or less granular, taking basic stains and coloring light blue with hematoxylin, and red or violet with polychrome methylene-blue. Occasionally the central portion stained intensely, and when the capsule was absent or indistinct, such organisms resembled small lymphocytes. In other organisms it remained unstained or presented the same color as the surrounding tissue. In the fixed and stained as well as the unstained organisms, one or more vacuoles may be present, but the most common feature in the former was the presence of small spherical basophilic granules, usually from three to ten in number. Although quite regularly arranged, their distribution in the cell cannot be said to be characteristic. They were often found in the budding forms and in some instances appeared to be contained entirely in the bud. The association of these granules with spore-formation has been suggested by a number of writers on this subject. According to most observers, proliferation in tissue occurs by budding. Hyphae have not been found in the tissues, and sporulation has been suggested in but one instance (Case 8), the extremely small size of the organisms and occurrence in clusters being the chief reason given. In old cultures a vacuolization occurs which strongly resembles sporulation.[7]

The blastomycetes grow readily on ordinary mediums. No difficulty was experienced in obtaining growths on sterile moist bread, paper, cardboard, cotton, sawdust, fruit and vegetables. Isolation from other organisms can usually be accomplished by making a thin stroke on a dry agar surface, the tendency of the blastomycetes to extend over the surface making it possible to obtain pure subcultures. In a few instances this was accomplished by spreading the suspected pus, diluted with bouillon, over a large area of sterilized bread.

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[7] In our studies, a process thought to be endosporulation was observed in one instance. In an agar-slant culture of a strain obtained from Case 19, sixteen months old at the time, a contamination occurred and the surface became covered with a slimy saprophytic growth. Examination of a smear before discarding disclosed the presence of a large number of round forms of blastomycetes scattered among the bacteria, which belong to the *Bacillus subtilis* group (Fig. 2). Budding and hyphal forms were absent. Bodies considered to be spores appeared in the organism as round clear objects which varied markedly in size and distribution (Fig. 3). Sometimes only one or two were present in a cell, but they usually occurred in large numbers, irregular in size. In some cases a fairly regular distribution was noted. The larger forms sometimes extruded from the cell, and in other instances the cell outline was lost in a zooglea-like mass of cluster of the smaller forms, similar to those observed in tissues. That these appearances were due to a reproductive rather than an involution process was assumed because of the innumerable small round forms present, the similarity, even to the refractile capsule, of the younger forms within the parent cell to those lying free in the neighborhood, and the absence of any other form of reproduction. The same process also was observed to a less extent in a subculture from the tube described above. It was impossible to isolate or obtain growths of the blastomycotic organisms in subsequent cultures, owing probably to the innumerable bacteria which were present.

A proliferation by budding, such as occurred in the body, is at first observed on mediums, but sooner or later the production of hyphae and myceliums characteristic of the mold growths occurs. Budding is favored by moisture and thermostat temperature, the other methods of growth by room temperature, dryness of the mediums and transplantation. The time required for the appearance of the hyphal form varies somewhat. In a few instances hyphae were noted in the first cultures made from the pus and kept at room temperature; in others the budding persisted for some time.

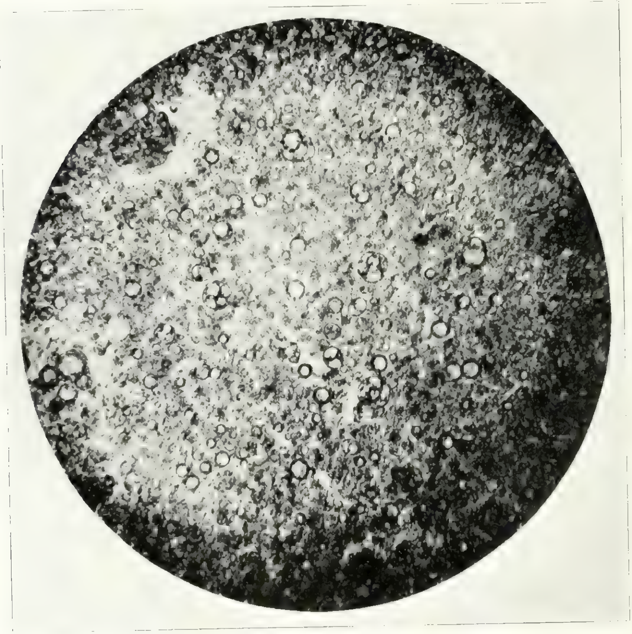

Fig. 2.—A preparation made from a blastomycetic culture which had become contaminated with *B. subtilis*. The innumerable small round forms suggest endosporulation.

The gross appearances of the cultures depend largely, as might be expected, on the method of multiplication, and many of the variations reported are undoubtedly due to the degree of transition from budding to other forms of growth present at the time of observation. As mycelial growth becomes more marked the budding forms are less numerous and often difficult to demonstrate; but even after months of growth of the mycelial type on agar, a few budding forms may be found in the deeper parts of the cultures.

The pure budding form (blastomycetoid type) may occur primarily in cultures from pus or may appear later under certain conditions as a reversion from the mycelial form. The colonies on agar were at first small and round and presented a pasty appearance. They varied in color from white to light yellow and were easily detached and broken up. Later as hyphae began to form, they assumed a waxy or porcelain-like appearance, became tough and adherent, and subsequently formed a surface membrane which in some tubes became nodular or rugose (Tubes *a* and *b*,

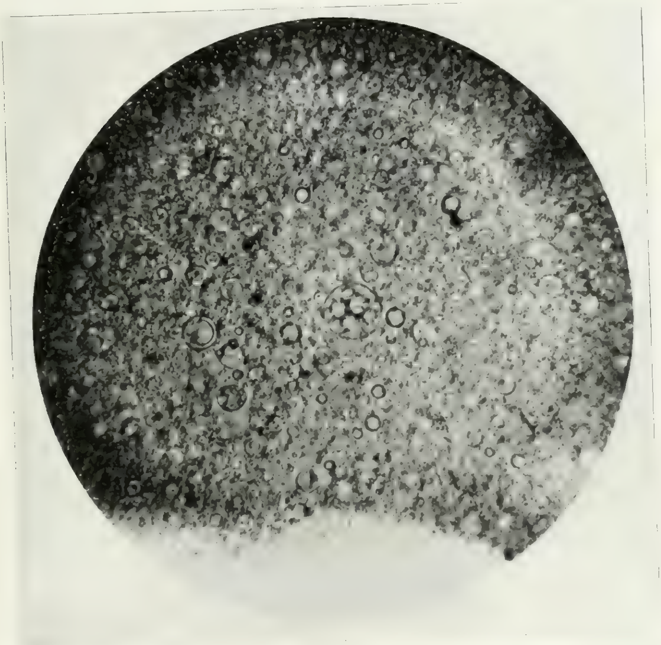

Fig. 3.—Endosporulation? Higher magnification. The innumerable small round forms are more plainly seen.

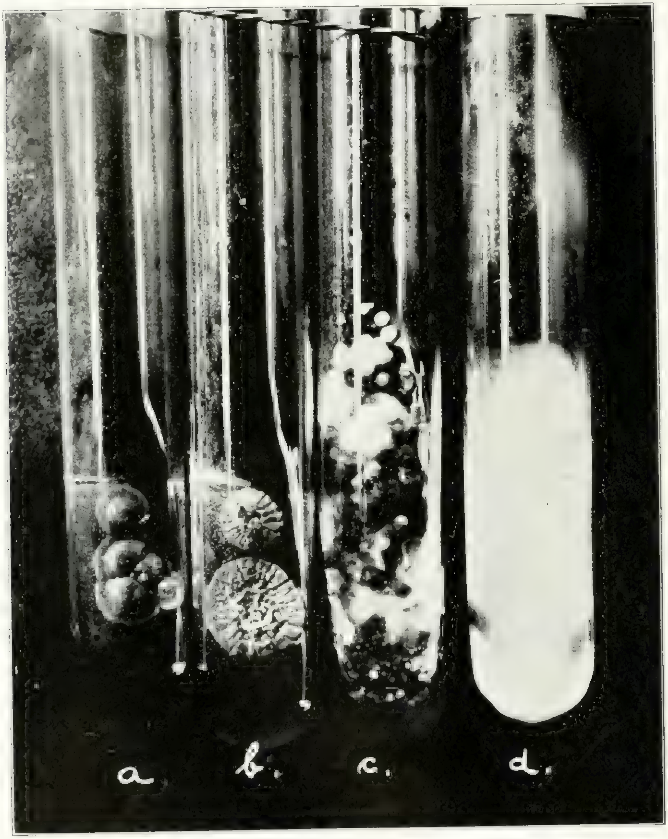

Fig. 4.—Cultures of blastomycetes. Type 1: (*a*, *b*) nodular and rugose appearance of colonies on glucose agar; (*c*) mixed forms — beginning formation of aerial hyphae causing white fluffy appearances; (*d*) characteristic white fluffy growth of the mycelium with aerial hyphae.

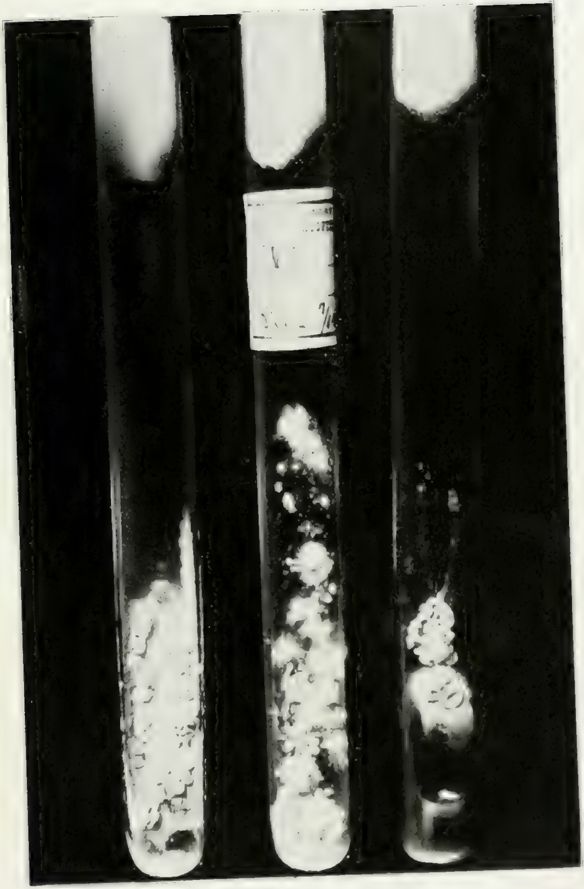

Fig. 5.—Cultures of blastomycetes Type 1, showing nodular, rugose and "bundle of worms" appearance.

Fig. 4), or assumed the "bundle of worms" appearance (Fig. 5). Subsequent cultures usually presented the characteristic mycelial growth (Tubes C, D, Fig. 4). It is of interest to note that such rugose or wrinkled surface membrane growths were more common during the fall and winter. Indeed, some of the strains which at room temperature during the summer grew abundant aerial hyphae, during the months of October and November grew these surface membranes which consisted principally of budding or short hyphal forms.

Single colonies of the mycelial type appeared as fine branching hyphae, radiating from a faint yellowish-white center. The hyphae grew into the mediums and also on and beneath the surface, increasing in number and extent until a membrane was produced. Viewed directly, such colonies appear as a moist fine, meshed or felted network of branching hyphae, having a slightly raised center. Viewed by transmitted light, the extent and manner of the growth of the refractile mycelium can easily be seen (Fig. 6). After longer growth the membrane may cover the surface and become very thick and adherent, the agar beneath often showing a brownish discoloration. In some cultures the hyphae may not become aerial, and proliferation occurs by the segmentation of the mycelium into spores. This corresponds to the oidium-like type of Rickett's classification. Later in the growth, however, or in the subsequent subcultures, the hyphae in the center of the separate colonies or on the surface of the diffuse growths become disengaged or raised from the surface and may bear lateral and terminal fruit-buds. This formation of aerial hyphae, giving the cultures the white, fluffy, mold-like appearance, occurred sooner or later in all the strains, and was for a time regarded as the final typical stage in the life of the organism (Tube D, Fig. 4). The aerial hyphae, at first short and thinly scattered over the surface, often become luxuriant, growing up the sides of the glass and sometimes filling the test-tube. In some cases aerial growth occurred in the first culture made from the pus. This form corresponds to the aerial or hyphomycetoid type in Rickett's classification. It will therefore be observed that the various forms described above, on which the classification of distinct morphological types was based, represent different stages in the life history of the organism. A gradual transition from the budding form (blastomycetoid) to the submerged and surface mycelial (oidium-like) growth, the hyphae of which later became aerial (hyphomycetoid), can be seen in any one strain, if observed for a sufficient length of time. These three forms, then, hereafter will be considered as variations of blastomycetes, Type 1, in contradistinction to Type 2, another form to be described, showing radical differences and representing, so far as has been observed, a possible final stage of growth or reversion type.

Glucose-lactose agar gave much more luxuriant growths than the plain agar. No differences could be observed in tubes of 0.6 per cent. acid, neutral and 0.6 per cent. alkaline reactions. Growths on potato, gelatin and serum agar showed no characteristic differences, except that on the latter, which contains glucose, the growth was more luxuriant and wrinkled surface membranes occurred more often.

Growths in bouillon inoculated with pus appear as fine sediment in the bottom of the tube, and in shaking can be seen to be finely granular. On examination, this consists of budding or short hyphal forms. Later, a number of round discrete mycelial tufts closely resembling thistle-down appear. In the test-tube these soon become confluent, forming a coherent mass, which can often be removed entire with the platinum wire. A single colony grown in the flask increased in size until it filled that part containing the medium, and retained its circular form. The older mycelium in the center of such large colonies undergoes a degeneration and becomes translucent, giving the growth a hollow appearance. When the mycelium reaches the top of the medium, a tough surface membrane is formed, on which aerial hyphae develop. Sometimes before the development of the latter the membrane sinks to the bottom, becomes brown and gelatinous, and finally disintegrates, while another may form on the surface. In subcultures, in which the transplanted material floats on the surface or remains adherent to the side of the glass, a surface membrane only may occur.

The form already mentioned as Type 2 appearing in subcultures of Type 1 was first obtained in a subculture on agar of an old bouillon growth of an organism from Case 22. In a rather diffuse growth of Type 1 a number of white small waxy colonies were observed and for a few days regarded as a contamination. When an attempt was made to remove them for examination, they were found to be very hard in consistency and quite adherent. The structure was mycelial in character and pure cultures were then obtained. The appearance of this mixed culture and also the first pure culture are shown in Figure 7. The character of this new type corresponded to the growth obtained from the blood in Case 19, and for this reason was considered to have some relation to Type 1. This type was afterward obtained from the cultures made from the pus in Cases 19, 20, 21, 22, 23, 25 and 26.

The time of appearance of the Type 2 is variable. It occurred immediately in cultures from the blood in Case 19, in five weeks in cultures (Type 1) from the pus in Case 25, and fifteen months in cultures from the pus in Case 18. Its occurrence seems to be favored by prolonged growth on liquid mediums and a gradual transition has been observed.

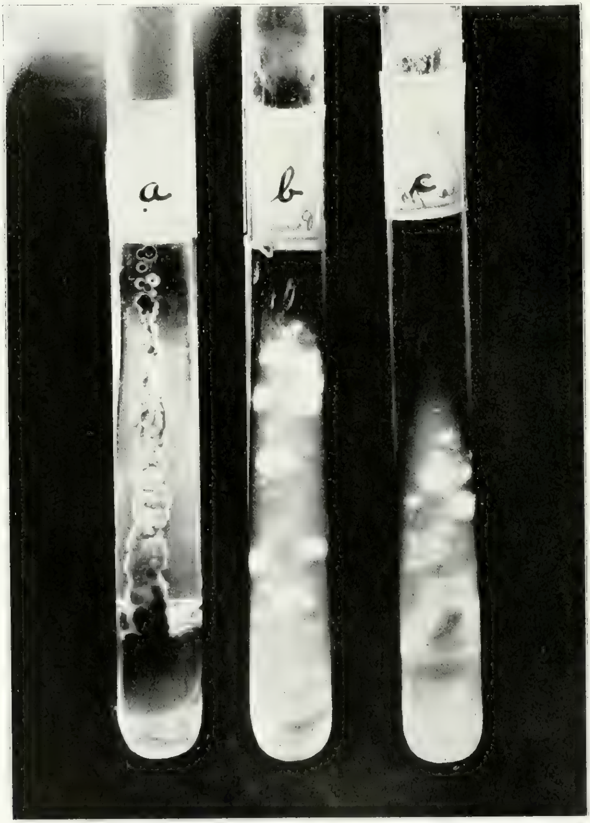

Fig. 6.—Blastomycetic cultures viewed by transmitted light: (*a*) Type 2; note the limited marginal growth of mycelium; (*b, c*) Type 1: submerged and surface mycelial forms whose manner of growth is more plainly shown.

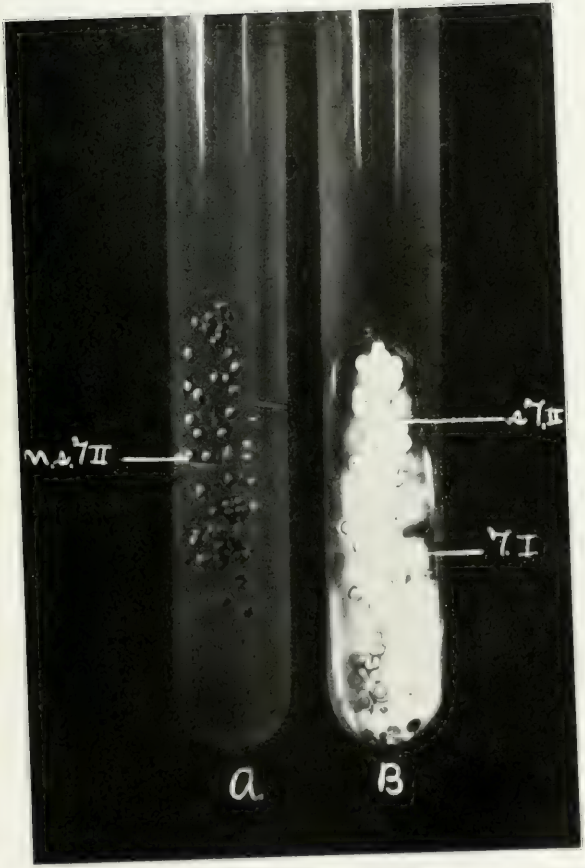

Fig. 7.—Cultures of blastomycetes obtained from pus: (*a*) non-sporulating form of Type 2 isolated form; (*b*) a culture of the usual Type 1 in which colonies of sporulating Type 2 (s T II) appeared.

On agar the colonies of Type 2 appear as round, glistening, opaque, white or yellowish growths, resembling closely those of staphylococci. They differ, however, in that they are tough and adherent. As the colonies become older they sink into the medium and the margins are depressed beneath the surface. Occasionally a cleft or circular opening appears in the center, giving a burst-bubble appearance. The next change observed in the same tube or in a subculture is a marginal growth of hyphae, which by transmitted light appears as a halo about the colonies (Tube A, Fig. 6).

With plenty of moisture at incubator temperature, the discrete colonies may attain a diameter of a centimeter or more, the surface then becoming moist, slightly granular and wrinkled. When the colonies become confluent a membrane is produced which, owing to the rapid central growth, becomes wrinkled or corrugated, similar to Type 1. The last, and so far as has been observed, the final stage, is the production of short hyphae bearing many small spores. The surface now presents a white powdered appearance (Fig. 8), although on glucose medium a gray has been noticed, and on several occasions a slight pink or red was observed. Glycerin medium, probably by preserving the moisture, seems to retard spore development. Reversion of Type 2 to Type 1 has not been observed. Type 2, then, so far as is known, represents the form finally assumed by the organisms after removal from the animal body, and is the form in which spore formation occurs to the greatest extent, resembling the natural molds in this respect. A minute portion of the spore form of Type 2 will produce innumerable colonies, whereas a considerable portion of the mycelium of Type 1 must be used to secure a growth. The possibility of obtaining the budding form by inoculation of animals with Type 2 is at present under investigation.

In cultures of Type 2 grown in bouillon the colonies are small, rarely attaining a diameter of more than a few millimeters. They usually remain discrete, and if they should become slightly coherent, separation readily occurs on shaking. In case any of the growths reach the surface a membrane also is formed, the surface of which assumes a white powdered appearance which is characteristic of the sporulating growths on agar. A distinct and characteristic musty odor is usually present.

Litmus Milk: The results of growths of either type on litmus milk were variable. In a few instances the milk became acid, but in the majority it was alkaline or unchanged. Coagulation occurred several times, but was not constant.

Fermentation Tubes: Both types of the organisms of the first five cases were tried with maltose lactose, dextrose and inulin bouillon, but no gas formation took place. All but two of them were tried later with dextrose and lactose bouillon with the same result.

The organisms resist drying for prolonged periods, growths having been occasionally obtained from dry cultures over eight months old. The presence of bacteria in the cultures seems, however, to inhibit the growth, and finally destroys the blastomycetes. The organisms are also readily killed by heat, 100 C. (212 F.), 1 per cent., dilution of liquor formaldehyd and chloretone, 0.8 per cent., and phenol (carbolic acid), 5 per cent. solutions. Sunlight and lack of moisture also inhibit the growth.

Morphology of Cultures: The morphology of blastomycetes Type 1 in cultures has been so well described and illustrated by other writers[8] that nothing of importance can here be added, and the structure of Type 2 is so minute that a detailed description is difficult to give. So far as has been observed, the mycelium corresponds in nearly all details to that of Type 1, except that it is very minute, the individual hyphae appearing as fine lines, with even the 1/12-inch lens. The spores appear very similar to cocci. Figure 9 shows fairly well the general appearance of the mycelium in contrast to that of Type 1 (Fig. 10, same magnification).

Experiments with animals to demonstrate the pathogenicity of the culture we isolated were not so successful as some reported by other observers. Dogs, rabbits, guinea-pigs, white and gray rats and white mice were used. The material inoculated consisted of pus aspirated from abscesses, and both fresh and old agar and bouillon cultures. The quantity varied from 1 to 7 c.c., and this was injected subcutaneously, intraperitoneally, intravenously and intratracheally. Death never was produced except when the cocci were present in the material inoculated. A number of white mice died apparently from the trauma of the injection. Subcutaneous inoculations usually produced abscesses, sometimes enormous in size, all of which healed spontaneously with or without rupture. Demonstration of the organisms in these abscesses and their cultivation was possible only during the first few days following inoculation. Injection into serous cavities or the veins produced a transient illness. Animals killed at varying periods after intravenous inoculation showed no microscopic systemic lesions. From agar-plates of the heart-blood of one rabbit killed two days after inoculation luxuriant colonies were obtained. I should conclude, therefore, that the lower animals are markedly resistant to blastomycotic infection in spite of its power to produce suppuration. It is possible that in the human being the resistance must be considerably diminished before infection takes place.

The obviously serious nature of the disease in man and the increase in the number of cases taken into the hospital naturally occasioned anxiety on the part of the attendants in regard to the possibility of contagion from the patient's sputum or the profuse purulent discharges, and the question of isolation arose. During the spring of 1908 a slight

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8. Ricketts, H. T.: Jour. Med. Research, 1901, vi, No. 3.

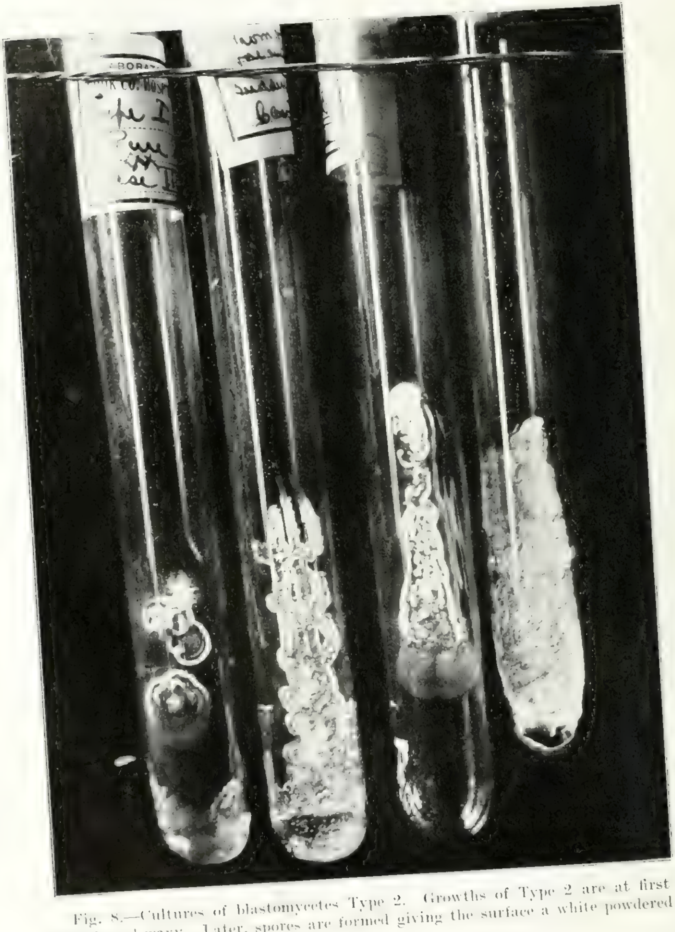

Fig. 8.—Cultures of blastomycetes Type 2. Growths of Type 2 are at first smooth and waxy. Later, spores are formed giving the surface a white powdered appearance.

nasopharyngeal infection was present among the hospital attendants. The throats of fifteen who had directly or indirectly been exposed to blastomycosis were examined. No organisms were found in the pharyngeal or bronchial mucus, nor were any cultures obtained. Strict isolation was not established, but reasonable precautions were observed. To our knowledge no one has been infected, and it is improbable that infection with the organism as it exists in the pus or sputum occurs except by direct inoculation. It may be advisable to mention at this point an incident which might have a bearing in the danger of handling the cultures.

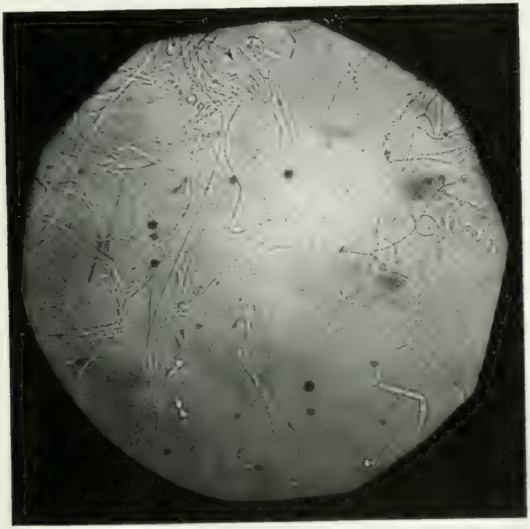

Fig. 9.—Photomicrograph of mycelium from a culture of blastomycetes Type 2. It presents the same general structure but is much smaller than Type 1.

During the laboratory work a test-tube containing a bouillon culture of blastomycetes (Type 2—sporulating) from the blood of Case 19, was broken in the presence of another person and myself. The odor was very irritating, and it is not improbable that a number of the spores were inhaled. In spite of sprays and an antiseptic gargle, a pharyngitis and laryngitis developed in one of us. The other experienced a chill about six hours later, and a purulent bronchitis developed lasting for three days, associated with considerable fever. No organisms, however, were obtained in films or cultures made from the sputum.

The resemblance of growths in cultures of these organisms to those of natural molds, and the ease with which (like the latter) they could be grown on moist bread (Fig. 11), cotton and various forms of cloth and paper, led to an investigation of the home surroundings of several of the patients as well as the conditions prevailing in such places when the disease began. The results are especially noteworthy, since in nearly all the reported instances in which the onset of the disease could be determined, it was learned that the first symptoms developed during the months when in this region great dampness and mold growth prevails.

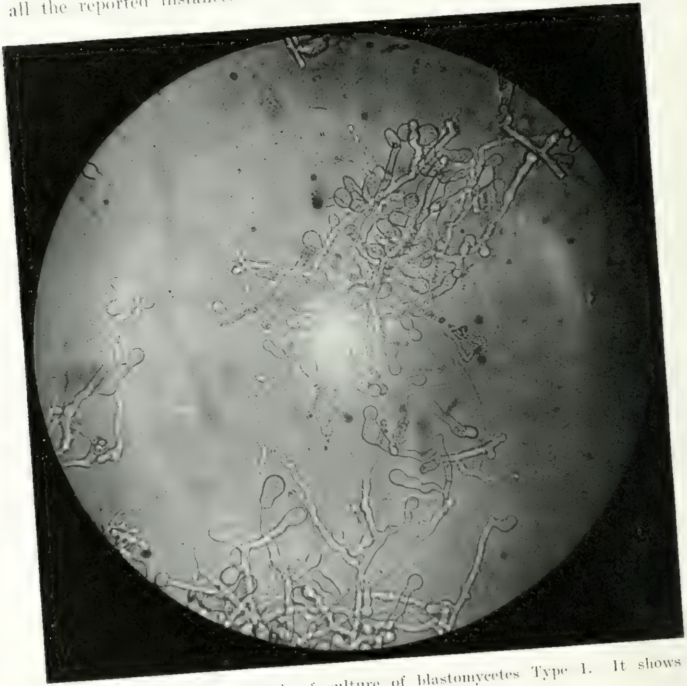

Fig. 10.—Photomicrograph of culture of blastomycetes Type 1. It shows plainly the budding and hyphal forms.

One patient (Case 19) lived in a basement on Huron Street. At the time of investigation it was uninhabited and entrance could not be effected. Through a broken window, however, the rooms were seen to be very dark. The floor was laid directly on the earth, and a number of the boards were completely decayed. From the neighbors it was learned that the family had very unhygienic habits, and that owing to lack of room the patient had often slept outside under the sidewalk. Another (Case 20) lived in South Chicago, also in a basement with a low ceiling and painted walls. The wooden floor was several feet below the level of the street, and the surrounding land was marshy and covered with pools of water. When examined (November) the rooms had been renovated and were in a fairly sanitary condition. The wife, however, stated that after the snow came and the ground was frozen, the floors were always

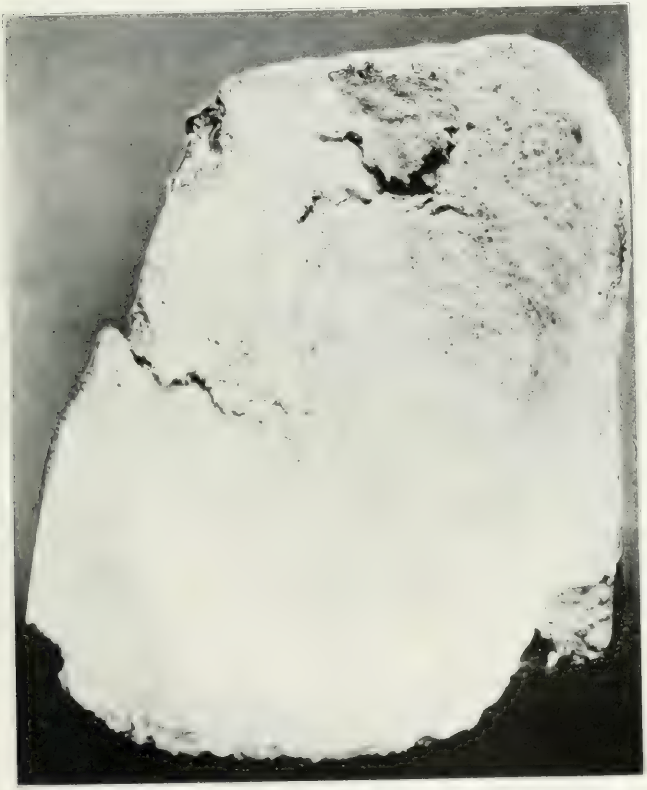

Fig. 11.—A loaf of bread three weeks after inoculation with blastomycetes Type 1. The mold has spread over the entire loaf.

damp, and that this was increased by the condensed steam trickling down the walls; also that the bed-clothes became so moldy that each spring they were forced to burn the mattresses. A third patient (Case 21) lived on the second floor of a three-story building. The basement, in which the closets of the tenants were situated, was dark, requiring the use of candles in the daytime. The floor of this basement was partially flooded with water, which was escaping from the sewer-pipes. The planks covering the floor were in various stages of decomposition, and presented much mold growth.

The fourth patient (Case 22) for six months prior to the onset of his illness had lived in a cabin-boat while engaged in dredging. A fifth patient (Case 23), during the winter he was infected, slept in a basement located in the "Ghetto" on the West Side of Chicago. It was low, dark and poorly ventilated. The wooden walls were backed with earth, quite moist in places and covered with a brown fungus growth. Where the wood was dry a white powder-like deposit was present (Fig. 12). The

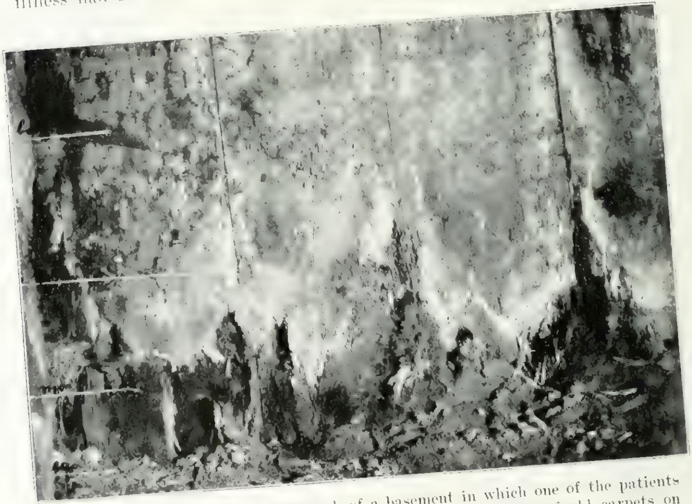

Fig. 12.—A flash-light photograph of a basement in which one of the patients slept during the winter he was infected. His bed was made of old carpets on a pile of sand near this board wall, which was banked with earth on the outside. For several inches above the point where the boards (*bo*) entered the earth (*ca*), a brown fungous growth (*mo*) was present. Above this, for some distance on the board the fungus was dry and the surface was covered with spores, giving it a white powdered appearance (*sp*). The growth was most luxuriant during fall, winter and spring months.

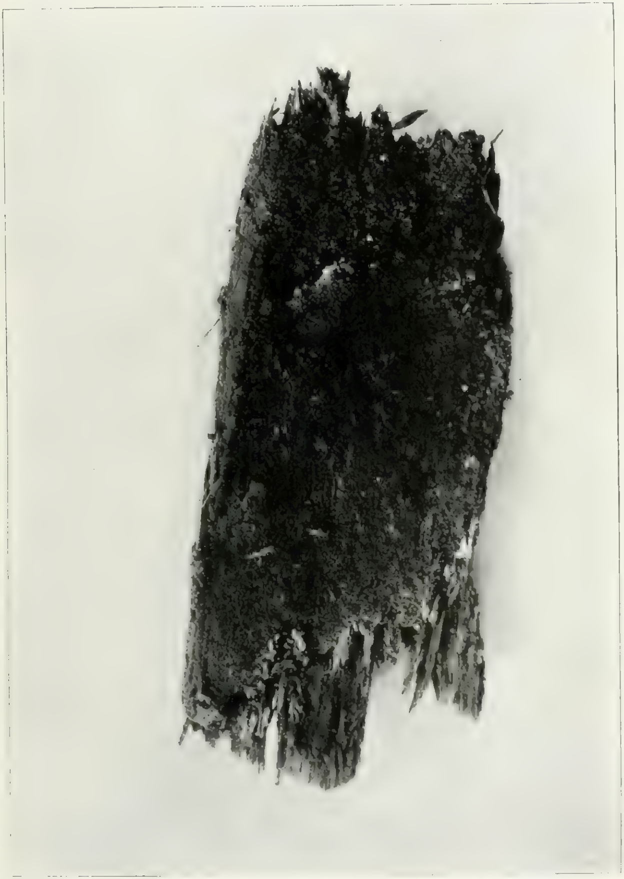

Fig. 13.—Fungus growth on a piece of wood removed from the basement illustrated in Figure 12.

patient slept on a pile of dirt near this wall, and his coverings consisted of several carpets which were also moldy. Several pieces of the decayed boards were removed and taken to the laboratory. The general appearance of the fungus growth was not unlike that of brown plush (Fig. 13). On drying the surface became covered with a white, powder-like deposit (Fig. 14). The same changes took place on the walls of the basement during dry weather. This powder when inoculated on agar gave pure cultures of a mold which differs in only a few respects from the blastomycetes, Type 2, to be described presently. Inoculations from the bouillon in which this fungus has been triturated also gave a large number of colonies of this type, and a few of another type. A low-power view of a section of the wood and attached fungus is shown in Figure 15. The general mycelial structure in which compartments of spores exist can be made out as the magnification is increased, and two varieties of circular bodies can be recognized[9] (Fig. 16).

A sixth patient lived near the lake in South Chicago, on the second floor of a two-story frame house built from 3 to 5 feet below the street-level and covered with water during the winter and spring. One small cooking-stove supplied the heat in winter for the rooms occupied by sixteen men. When examined in August the room, which had painted ceilings, was dry and well aired. During the drought of July and August, 1908, the dirt floor of this basement was still wet, and white mold spores were found on the timbers.[10]

The residence of a seventh patient (Case 25) could not be located. It was learned, however, that he had lived in the Croatian colony in South Chicago for three months. The dwellings there are old frame houses built on ground so low that the first floor is 3 feet below the street level.

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[9] 9. The first is a clear, round, translucent body, and is the variety which is most abundant. They are produced by segmentation of the hyphae, and probably constitute the spore form. The second variety is larger and usually dark brown. A few of these can be seen in the surface mycelium, but they are most abundant in the substance of the wood. Some appear to be formed in the hyphae, and in other places the hyphae seem to originate from them. Except in color they resemble closely the blastomycetes found in pus. In Figure 17 the double contoured round and budding forms can be seen distinctly. A teased specimen of the surface mycelium shows branching and segmentation similar to that observed in cultures of blastomycetes (Fig. 18). The first-mentioned cultures differ only from blastomycetes in that the growth is more rapid and luxuriant and that a red color appears in the growths on glycerin-agar, although a slight pink has been observed in the growths of Type 2 obtained from the blood-cultures. The second variety obtained from the wood resembles Type 1 in appearance, but it bears abundant elongated or cigar-shaped spores. In later cultures these spores become round. Photographs of these cultures are seen in Figure 19. Note resemblance to cultures of blastomycetes (Figs. 4 and 8).

[10] 10. Some of the material was removed to the laboratory, and nearly pure cultures of a mold resembling those already mentioned were obtained.

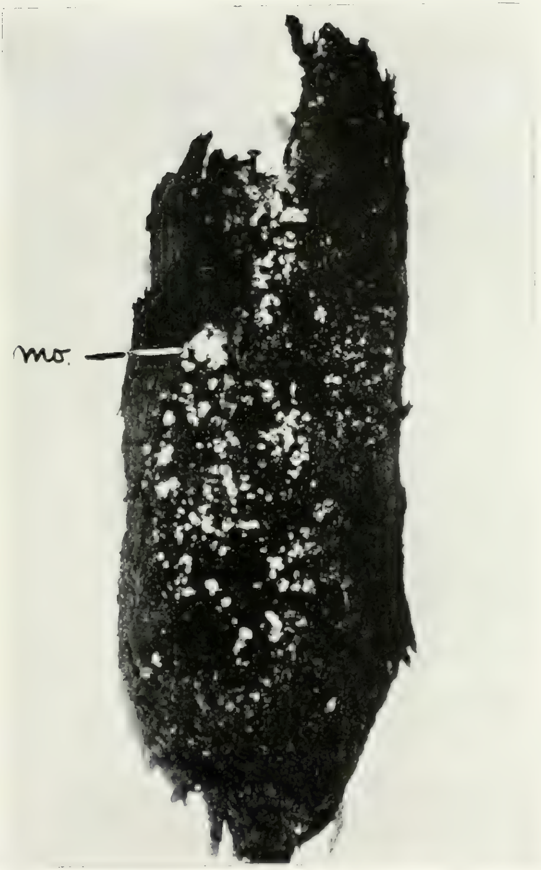

Fig. 14.—Another piece of wood from the same basement. The photograph was taken several weeks after it was removed to the laboratory and shows the numerous areas of white fluffy mold (*mo*) which appeared.

An eighth patient (Case 26) lived on the North Side, on the second floor of a two-story frame building; the first floor was used as the washroom of a steam laundry in which the patient worked. The floors were old and necessarily damp. No molds were discovered in this room, but in an adjacent closet a profuse mold growth was found on the floor. Immediately under the window of the bedroom was a small shed used as a storeroom, and often frequented by the patient. The floor at the time of investigation (July) was covered with litter which was damp and moldy. The occupants stated that during the fall, winter and spring, water was always present under the floor and could be forced up between the cracks of the boards by the weight of the body. Two barrels of decaying manure stood just outside the door.[11] No mold could be found in the living-rooms upstairs. It was learned, however, that during the winter the walls were always wet from the condensed steam of the laundry

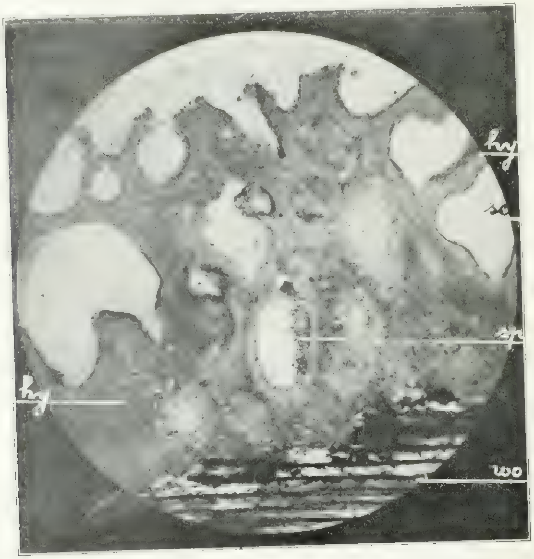

Fig. 15.—A low-power field of a section of the fungus illustrated in Figures 23 and 24: (*wo*) wood fibers; (*hy*) mycelium made up of hyphae enclosing (*sc*) spore compartments; in the latter are a large number of (*sp*) spores.

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[11] It is noteworthy to mention that one of Dr. Ormsby's patients at the time of infection slept in a room, the windows of which were located just above a manure-pile.

below. The bedroom was so small that there was room only for the bed. The only window was the one mentioned as located just above the shed and manure barrels. Specimens of moldy wood and leather from the shed and closet were taken to the laboratory and cultures obtained which resembled those already described.

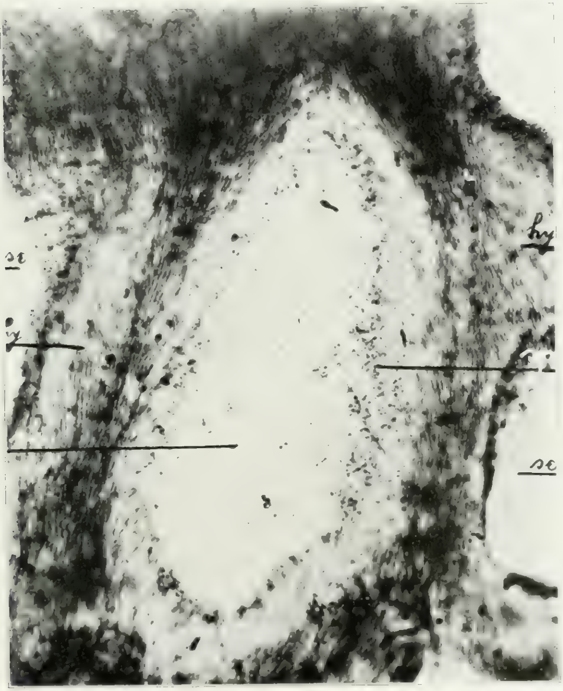

Fig. 16.—A higher magnification of the wood mold showing more plainly the (*hy*) branching segmented hyphae, (*sc*) spore compartments and (*sp*) spores.

The patient with cutaneous blastomycosis, mentioned subsequently, lived in a house the walls of which were constantly damp during wet weather. The roof leaked to such an extent that it was necessary to provide vessels to catch the water. He did not remember having seen any mold in the house, but states that musty or moldy odor was always present.

In view of the uncertainty expressed in botanical literature as to the closely related organisms, and because no one has undertaken to determine the final place the blastomycetes shall occupy in the systemic mycology, it is hardly pertinent to more than suggest that like other molds these organisms may possess a native habitat in such insanitary dwellings as those from which these patients came. It would also be hazardous to do more than suggest an identity between the molds grown from decaying boards and walls in these dwellings and the blastomycetes, although in many respects points of similarity were demonstrated, such as morphology, cultural reaction, pathogenicity and vaccine reaction.[12]

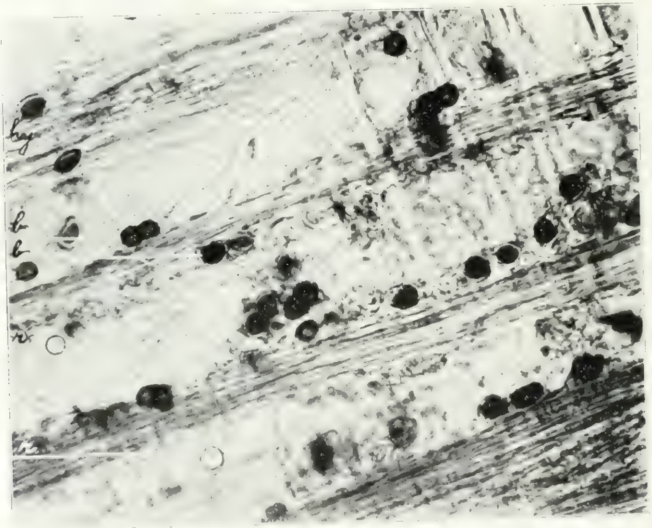

Fig. 17.—Photomicrograph of the wood just underneath the fungus, showing round (*r*) and budding (*b*) forms of organisms with refractile outlines. Segmenting hyphae (*hy*) can be seen running parallel to the wood fibers.

The suggestion of infection from these natural sources by inhalation is perhaps justified to a certain extent in that it is generally held at present from both the clinical and pathological evidence that the respiratory tract is the atrium of infection in systemic blastomycosis. In at least fourteen of the cases reported the first symptoms were referable to the lungs, and of eleven necropsies in these cases, nine presented old bronchopneumonic lesions. It is also possible that the subcutaneous abscesses or cutaneous lesions marking the onset in other patients were due to unrecognized pulmonary lesions with metastases in the skin and elsewhere. In man no very good evidence of infection of the intestinal tract has been obtained. In four cases of this series the Peyer's patches were reticulated and pigmented, and in two cases the mesenteric lymph-nodes were enlarged. In another case (Case 7) peculiar nodes were found in the colon and regarded by the authors as blastomycotic; organisms, however, have not been demonstrated in either the bowel or mesenteric lymph-nodes.

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[12] See Case 6, vaccine therapy, also in a subsequent discussion in this article.

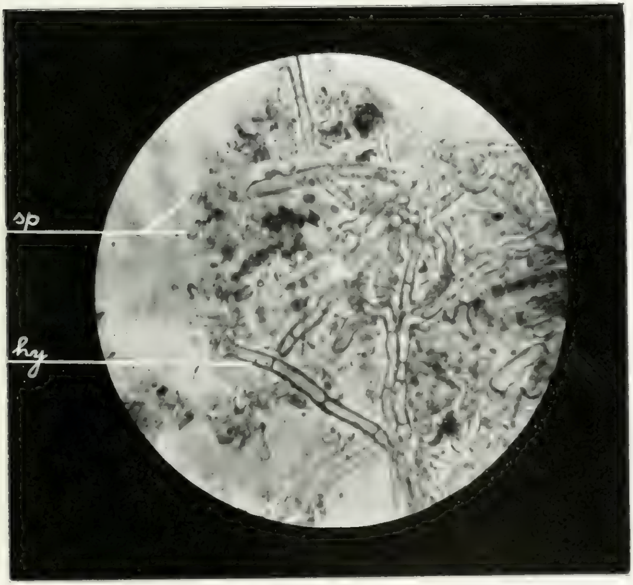

Fig. 18.—A teased bit of mycelium from the wood mold showing the segmentation of the branching hyphae (*hy*) and the round spores (*sp*).

As for infection of the skin, such a large number of cases of cutaneous blastomycosis have been reported that this condition is no longer regarded as uncommon. In some of these it seems quite evident that the infection followed some form of traumatism. In only three instances, however, has it been clearly established that systemic infection followed, and in these, the cutaneous lesions existed for from seven to twelve years, respectively, before symptoms of systemic blastomycosis were manifested. In once case (Case 12) the infection occurred several months after cutting the foot on a clam-shell. That direct inoculation does occur was established in two of our cases in which new superficial lesions developed in the abrasions resulting from scratching. Blastomycetes were found in the detritus under the finger-nails of these patients and undoubtedly had origin from preexisting ulcers which the patients persisted in scratching.

Pathology: The skin and lungs have already been mentioned as constituting the principal atria of infection. The spread of the organisms from these points and the resulting pathological conditions depend very much on the resistance of the individual and the location of the primary lesion.

Dissemination of organisms from cutaneous lesions does not seem to have occurred very often. These lesions have considerable tendency to spread by contiguity of tissue, but invasion of adjacent lymph-nodes is not common, and in only a few instances have the organisms entered the blood-stream, producing metastatic lesions in the lung and systemic infection. In two cases this process seems to have followed directly the curettement of the cutaneous lesions.

Primary infection of the lungs, as pointed out before, appears to occur first in the bronchi, to be followed by the development of areas of bronchopneumonia in the neighborhood. Further lymphatic spread is possibly responsible for the pleuritis, pericarditis and mediastinal lymphadenitis which have been noted. From these lesions in the lung, organisms may enter the blood and become distributed throughout the system with the production of multiple metastatic foci, which in turn may give rise to further dissemination by the blood route and reinfection of the lung. The repetition of these processes may thus constitute a vicious circle and afford ample explanation for the numerous metastatic lesions characteristic of this disease. The skin, muscles, subcutaneous tissues and the bones of nearly every part of the body have been involved, and all of the important viscera have presented more or less evidence of infection.

The variation in the reaction of the tissues to the presence of the organisms noted in a single case are most remarkable. Blastomycetes in considerable numbers were not uncommonly found associated with no histological change whatever. In other instances slight necrosis was the only alteration noted.

The majority of the infected areas, however, presented round-cell infiltration, either alone or associated with giant-cells, polymorphonuclear leukocytes, or both. In some tissues, especially in the viscera, in which the lesions were small, definite nodules were found and closely

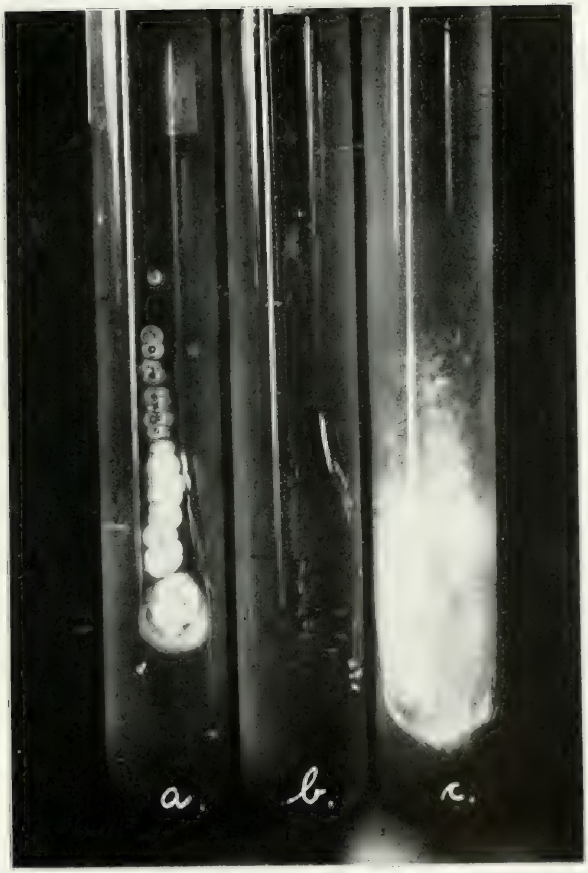

Fig. 19.—Cultures made from the wood mold gave a large number of colonies (*a*, *b*) closely resembling those of blastomycetes Type 2 obtained from blood and pus. A few colonies resembling blastomycetes Type 1 were also obtained and shown in tube (*c*); (*a*) and (*b*) are the same, except that the former is the older culture and sporulation has occurred, giving it a white powdered appearance.

resembled those found in tuberculosis except that central necrosis was less marked. Other nodules contained many polymorphonuclear cells constituting small abscesses. These were found either discrete or confluent, the latter being separated by blood-vessels and bands of compressed tissues. Some were very small, occupying an area equal in diameter to one-half of a high-power field. The larger abscesses were often surrounded by a distinct wall of granulation-tissue. Giant-cells usually were present, often in considerable numbers. Their absence in a few instances was especially noted. They were usually of the Langerhans type, but were rarely as typical as those found in tuberculosis. In some cases healing of the infected areas occurs and is often associated with marked fibrosis, especially in the skin, lungs and pleura.

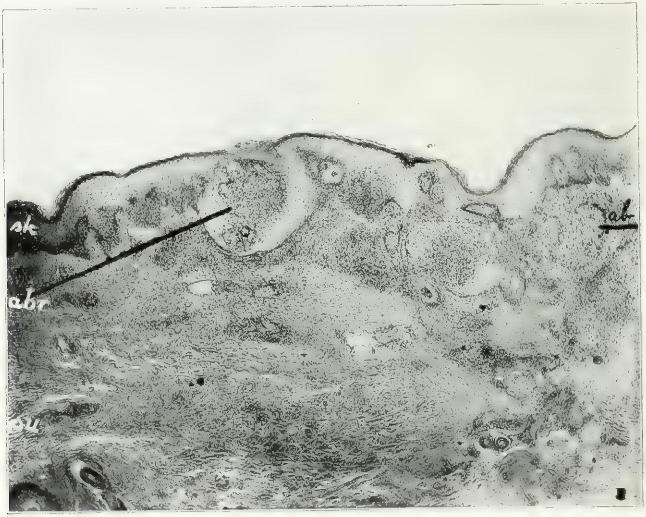

Fig. 20.—A section showing blastomycotic abscesses in the skin and subcutaneous tissue: (*sk*) skin, the epithelial layer of which has been involved secondary to (*ab*) the subcutaneous abscesses; (*abr*) an abscess about to rupture; typical cutaneous lesions often develop at these sites.

The changes most characteristic of blastomycosis are the cutaneous ulcerations, the deep and superficial abscesses, and the often tubercle-like nodules in the viscera. Some of these lesions deserve special mention.

The infections in the skin may appear as pustules, subcutaneous abscesses or local ulcerations (Figs. 20 and 21). The pustules are usually multiple and may occur successively or in crops. The ulcers may occur primarily as such or develop in the site of the ruptured abscesses. In cases of the latter, the ulcer produced is usually surrounded by an areola of inflammation: the margins are slightly raised and irregular, and the base is soft and covered with granulation-tissue, which may become fungoid and approach the surface, later assuming a papillomatous appearance, which is more or less characteristic of the lesions of chronic blastomycosis of the skin (Fig. 22).

The abscesses may be superficial or deep and have origin in the skin, subcutaneous tissues, lymph-nodes, muscles, bones, nervous tissues and viscera. Their size is most variable, ranging from very minute areas to enormous cavities containing a quart or more of pus. Those having origin in the deeper tissues are more or less hard at first, but fluctuation develops sooner or later. Some are associated with pain and the signs of inflammation, whereas others are discovered by the patient accidentally. Spontaneous healing of even large abscesses was noted, but the majority either ruptured or required incision and drainage to relieve the tension pain. Healing then took place, or a discharging fistula persisted, the opening of which sometimes became surrounded by the char-

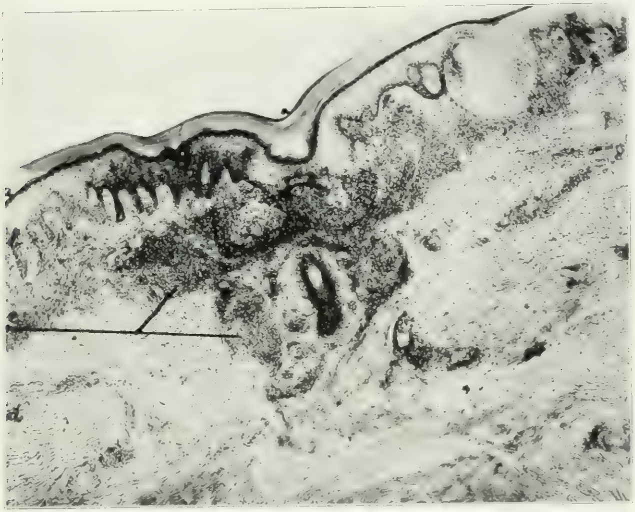

Fig. 21.—Photomicrograph of a section of subcutaneous abscess: (*a*) stratum corneum; (*b*) papillary layer which is being invaded by (*c*) the abscesses containing large number of blastomycetes; infection here occurred from the blood; (*d*) subcutaneous tissue.

acteristic papillomatous ulceration. The pus usually was thick and tenacious, making aspiration difficult, and varied in color from a light yellow to a dark red or brown, according to the amount of blood present.

Blastomycetes can usually be demonstrated in the pus by mounting it direct or mixing with a 20 per cent. solution of sodium hydroxid (Fig 1). In a few instances they could not be demonstrated either in smears, tissue sections or by cultures. Perhaps the most reliable method in such cases is the staining of a thin smear on a slide with hematoxylin and eosin, or with polychrome-methylene-blue. The degenerated forms can then be more easily recognized.

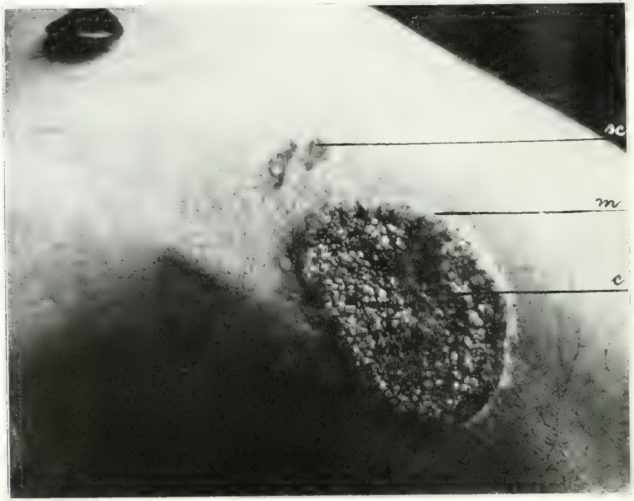

Fig. 22.—A typical lesion of cutaneous blastomycosis: (*c*) papillomatous or verrucose surface; (*m*) raised indurated border containing miliary abscesses; (*sc*) scar of old lesion. (By courtesy of Dr. O. S. Ormsby.)

The affections of the bone consisted of osteomyelitis, periostitis and arthritis. The osteomyelitis which is suppurative in its nature may be diffuse[13] or localized. In either case the fungi are very numerous, invading the narrow compartments and causing necrosis of the marrow cells, with the formation of a purulent exudate.[14] The bone partitions then disappear, the areas become confluent and an abscess is thus produced. The process may involve the bone to such an extent that spontaneous fracture happens. Ruptures of these abscesses often occurred, causing extension to adjacent tissues. Such lesions in the ribs,[13] clavicle, sternum,[15] the bones of the skull, and the small bones of the hands and feet were important features in a number of cases. Formation of sequestra was observed in two instances.

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[13] Figure 2, Case 19, article by Krost, Moes and Stober, this issue.

[14] Figure 4, article by Krost, Moes and Stober, this issue.

In the long bones the infection has a tendency to lodge in the epiphyses,[16] and in some instances the shape of the infected areas strongly resembled those produced by infarcts.[17] Extension by rupture of the epiphyseal abscesses was responsible for the majority of the joint lesions.[18]

In those necropsies in which opportunity was afforded to study the changes in and about the joints, communication with abscesses in the adjacent bone were always found. In the cases in which suppuration of the joint was marked, more or less destruction of the synovial membranes, the articular ligaments and periarticular tissues was produced, often to the extent that subluxation occurred. The articular cartilages were sometimes so completely destroyed that the rough eroded bone was exposed.[19] Diffuse blastomycotic osteomyelitis of such an exposed head of the tibia was found in Case 21.[20] A healing periostitis was also present in this case. Special mention should be made of the spinal lesions because of the close resemblance of the symptoms produced to those of tuberculosis or Pott's disease. Spondylitis was present in Cases 7, 8, 18, 19, 23 and 28. The bodies of the vertebrae were affected in all except Case 23, in which the disorganization seemed to have occurred in the laminae and the posterior ligaments. More or less complete paralysis occurred in two cases.

A careful study of the appearances of the bone lesions in numerous roentgenograms was made by Dr. H. E. Potter, roentgenographer to the Cook County Hospital, and the following are his observations:

> In general the presence of blastomycotic infection of bone is easy of demonstration on account of the intense localized nature of the destructive process. In the first stages of the invasion no changes are visible; but as soon as destruction and absorption have advanced to a moderate degree the lesions are easily demonstrable. On the whole it has been our experience that the radiographic findings are more marked than in other types of infection presenting a similar clinical picture. Moderate pain, tenderness and swelling around a joint may be accompanied by a marked degree of bone involvement.

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[15] Figure 1, article by Krost, Moes and Stober, this issue.

[16] Figures 4 and 5, article by Lewison and Jackson, this issue.

[17] Figure 4, article by Myers and Stober, this issue.

[18] Figure 3, article by Myers and Stober, this issue.

[19] Figure 2, article by Lewison and Jackson, this issue.

[20] Figure 4, article by Lewison and Jackson, this issue.

I have been fortunate in being able to obtain numerous skiagraphs at various stages of the disease from cases which were being studied exhaustively from a clinical and pathologic standpoint. The lesions which were skiagraphed and studied occurred in the spine, ileum, ribs, femur, tibia, fibula, scapula, humerus, radius, ulna, and in the wrists, hands, ankles and the feet. The following conclusions have been drawn from a serial study of the plates alone.

Skiagraphs of blastomycotic bone lesions show rarefactions and osseous proliferations not dissimilar in some respects to those seen in other types of bone infection. A comparative study of more than a score of these lesions in their different stages and degrees of activity has shown, however, that certain appearances are quite constant in blastomycosis and but seldom seen in other affections.

The lesions are most numerous and distinct in the long bones. Here they are first seen in the spongy portion near the epiphysis (Fig. 23) or, if the extremity bears no epiphysis, they lie in close relation to the articular surface (Fig. 24). A focus may remain single or others may appear in the vicinity, coalescing as they increase in size. Coincident with rarefaction a bony periostitis develops over the extremity of the diaphysis and may completely envelope it. The newly formed bone may in turn undergo a progressive dissolution as the inner necrosis advances, although an instance has been observed (Case 24) in which an arrested rarefaction was followed by a complete and persisting encapsulation.

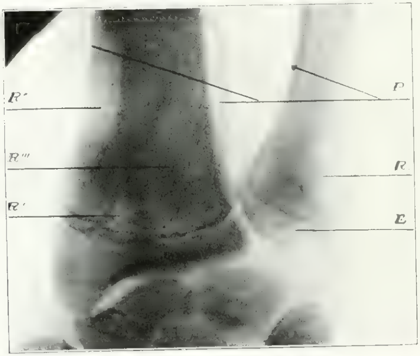

Fig. 23.—Lower end of radius and ulna. *R*, an early focus in ulna beneath epiphysis (*E*). R′, R″ and R‴ are early foci in radius. *P*, periosteal ossification.

The epiphysis remains quite uniformly intact unless the joint cavity has been involved; erosions are then seen on the articular face. The compact bone of the shaft has shown erosions on its surface secondary to a deep abscess in the overlying soft tissues. Such a bone destruction in the shaft may give the appearance of a primary focus within the bone, until a projection at another angle proves it to be superficial. I have not seen a case in which the attack on the compact bone from without has led to a penetration with the formation a medullary abscess.

In an involvement of the short bones, which indeed is quite common, the picture is that of multiple foci, general osteoporosis, and early invasion of adjacent joints, with a minimum of bony proliferation.

The usual appearance of well-marked necrosis and opposition seen in the ordinary lesions of the long bones is modified in those cases in which the clinical course has been acute and in those which show a tendency to subside or heal. The former show gross destruction and limited proliferation, while the latter show a much greater proportion of newly formed bone. In an extremely rapid process the destruction may be complete, while the only evidence of opposition is seen on the shaft above the site of necrosis.

The bone surrounding the ordinary blastomycetic focus presents a normal structure with little tendency to change in density. This gives a rather sharp line of demarcation between bone apparently intact and regions of total necrosis. Such a marked localizing destruction occurring within the spongy bone of a diaphysis together with a mature and homogeneous periosteal proliferation with or without cloaca, is so constantly present in the ordinary lesions of blastomycosis that when seen in further skiagraphs where the etiology has not been determined, a careful search for blastomyces should be made.

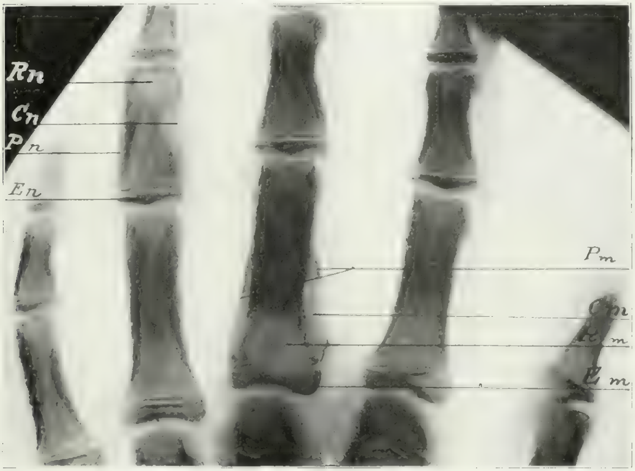

Fig. 24.—Phalangeal involvement: *m* shows coalescing foci beneath epiphysis (*Em, En*); *cm* shows a secondary breaking-down of proliferated bone (*Pm, pn*); *Rn*, a rarefication at a non-epiphyseal end of second phalanx. The same general characteristics are shown. A softening of the proliferated tissues at *Cn* is distinct. The adjacent joint is normal.

The pathological changes found in the respiratory system of eight patients in this series conform in a general way to those described in the eight previous reports of post-mortem examinations. Acute laryngitis and bronchitis were usually associated with active pulmonary lesions, and the pleurae also presented changes in accord with those found in the lungs. In cases with active pulmonary lesions, a serofibrinous pleuritis was quite a common finding and in one of our cases (Case 20) blastomycetes were isolated from the exudate. In other cases fibrous pleuritis was present, often obliterating the cavities. The thickening of the pleurae at times was remarkable,[21] and the scars at the apices usually involved the adjacent tissues for some distance, in one case causing constriction of the jugular vein. Pus in the pleurae occurred but once, this in a localized empyema found in Case 19. Fistulous passages in the pleurae extending to a lesion of the spinal column were found in one of our cases (Case 23) similar to that observed in Case 7, and communication with the left bronchus was noted in Case 22.

A comparison of the lesions found in the lungs in these post-mortem examinations with those of eight previous reports, as mentioned before, suggests two methods of infection. In a few cases the bronchogenic type predominated, but the majority showed diffuse hematogenous infection, the primary foci existing as fibrous areas about the larger bronchi.

In the bronchogenic type much fibrous tissue existed, either solid or enclosing regions of infected lung tissue and usually located in the upper lobes.

In one case an upper lobe was converted into a fibrous mass in which were areas of necrotic material, some of which were associated with cavity formation and dilatation of the bronchi.[22] In marked contrast to such extensive fibrosis was the small area found in the lung of Case 21.[23] This represented the only change in the lungs of a patient who a few months before had presented clinical evidences of wide-spread pulmonary infection. The recent lesions consisted of small foci which have already been described as characteristic of blastomycosis; although in some cases distributed throughout the lobe or lung, they were quite discrete, and histologically such areas were often found unassociated with inflammatory changes in adjacent alveoli.[24] This may explain the indefinite physical signs which were obtained in the examination of lungs which at necropsy were found to be extensively involved. In other cases such foci had become confluent, forming larger areas of consolidation which were usually light gray.[25] Softening in the center of such areas was occasionally present. These focal lesions in some cases were distributed in such a manner as to suggest a bronchogenic origin.[26] In other cases, however, the wide-spread and uniform distribution closely resembled a miliary tuberculosis and could hardly have occurred except as a result of infection through the blood-stream. In the more severe cases the infection was so marked that complete consolidation of the lung was produced, although here and there small nodules could be seen.[27]

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[21] Figure 7, article by Krost, Moes and Stober, this issue.

[22] Figure 1, article by Myers and Stober, this issue.

[23] Figure 3, article by Lewison and Jackson, this issue.

[24] Figure 3, article by Churchill and Stober, this issue.

[25] Figure 3, article by Krost, Moes and Stober, this issue.

[26] Figure 1, article by Boughton and Clark, this issue.

Concerning lesions in other viscera our observations also correspond to those in previous reports in that focal infections were quite common in the spleen, liver and kidney.[28] Foci in the myocardium (Case 6), adrenal (Case 6), and pancreas (Case 5) had been found but once, and to this we are able to add instances of infection in the pericardium (Case 20) the adrenal (Case 26) and pancreas as well as four cases of blastomycotic abscesses of the prostate[29] (Cases 19, 20, 26 and 29), two of which were undoubtedly the source of the organisms found in the urine. Nephritis was more or less marked in all cases, myocarditis in a few, and acute endocarditis in one case (Case 21).

While lesions elsewhere have been quite numerous it is worthy of note that involvement of the brain has previously been noted but once. In the report of Case 7 a large abscess in the cerebellum together with lesions of the spinal dura and cord are described, and subsequently small lesions in the cerebrum were also discovered. In the four cases of this series (Cases 19, 21, 22 and 26) in which complete examination of the brain could be made, local lesions were also found. They consisted of small abscesses of variable size and location. In cases 19, 22 and 26 they were found in both cerebrum[30] and cerebellum,[31] and in Case 21, one solitary nodule was found in the pons. These have been discussed by Dr. LeCount.[32] The external cerebral dura was affected by extension of a bone abscess in Case 20, and the patient in Case 2 died of a meningitis, the blastomycotic nature of which was not determined. Such a process, however, had been anticipated and was found in the necropsy in Case 27 by Dr. LeCount. The spinal cord also was involved in Cases 18 and 23.

Of considerable interest is the existence of lymphadenitis in blastomycosis inasmuch as the slight tendency of the blastomycetes to invade the lymph-nodes has been dwelt on as a differential point between this infection and coccidioidal disease. A general enlargement of the lymph-nodes was found at necropsy in about one-third of the cases, and blastomycotic lesions in addition to having been found in the peribronchial lymph-nodes a number of times were on two occasions in this series also found in the submaxillary, axillary and inguinal lymph-nodes.

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[27] Figure 1, article by Churchill and Stober, this issue.

[28] Figures 2 and 5, article by Myers and Stober, this issue.

[29] Figure 2, article by Churchill and Stober, this issue.

[30] Figure 6, article by Myers and Stober, this issue.

[31] Figure 7, article by Myers and Stober, this issue.

[32] LeCount, E. R., Jour. Nerv. and Ment. Dis., 1909, xxxvi, 144.

As a final supplement to the list and perhaps worthy of mention is the general infection of the eye which occurred in Case 20. Blastomycetes were obtained in pure culture from the vitreous humor, but no opportunity was afforded to study the pathological changes.

In a majority of the cases in which a careful history could be obtained, the patients stated that their illness began with a cold or an acute infection of the respiratory tract, more or less intense in degree. The more intense infections were sometimes preceded by a chill, and the symptoms most often noted were pain in the chest, fever, dyspnea, cough and expectoration of bloody and purulent mucus, to be followed sooner or later by the occurrence of the characteristic subcutaneous abscesses. In other cases the onset was less abrupt and the initial symptoms slight and transient, the first manifestations to attract the patient's attention being the appearance of the local ulcerations or abscesses.

After the disease became established the general symptoms were those of a chronic infection: malaise, loss of strength, emaciation, pain in the affected parts, irregular fever, rapid pulse and occasional chills and sweats. Emaciation and loss of strength were usually proportionate. In our cases the emaciation was extreme. The face became drawn and haggard and assumed an expression which impressed the observers as being somewhat characteristic. The enlargement of the affected joints presented a marked contrast to the emaciated extremities.[33]

The temperature was most irregular, sometimes high, and at other times normal or subnormal. In general, however, a fairly regular evening rise of temperature was present, and was usually associated with profuse perspiration. In one case the high temperature occurred in the morning. The pulse was usually increased in rapidity and often out of proportion to the temperature.

Symptoms of pulmonary infection occurred sooner or later in all, and in some constituted the principal manifestation, although in no cases were the symptoms or physical findings commensurate to the extensive lesions found in the lungs at necropsy. Cough was usually present, sometimes severe. The sputum was thick and purulent or mucopurulent in character, often containing blood. The latter was present in nearly all cases, but was irregular in occurrence and small in quantity. No marked hemorrhages occurred. Blastomycetes were present in the sputum in eight of the cases of this series, and in the mucus removed from the trachea at necropsy in the other two. They were also noted in the sputum in four of the other reported cases.

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[33] Figure 1, article by Wewison and Jackson, this issue.

Their demonstration is quite easy when examined in 20 per cent. solution of potassium hydroxid with a 1/8 inch objective (Fig. 25).

Respirations were increased, and in a few cases dyspnea and hoarseness were present. Sharp pains in the chest, due probably to the acute pleuritis, were not infrequent, but they rarely lasted more than a few days. The majority of the patients complained of a dull aching sensation in the chest. Of the physical signs, diminished expansion of the chest, due to fibrous pleuritis, was often found. Dulness on percussion, the presence of râles, and increased transmission of breath and voice sounds were frequently noted, but as already stated, were not present in a degree proportionate to the changes found in the lungs at the post-mortem examination. Areas of consolidation occurred first as a rule in the apices or upper lobes of the lungs, the right side being affected about three times as often as the left. Râles over the bases with no definite signs of consolidation were not infrequent. Very little gastro-intestinal disturbance was noted. Anorexia was a common feature, and diarrhea was present in five patients. Blastomycetes were found twice in the feces. The spleen was not constantly enlarged. Nephritis was not uncommon, and in several cases a marked edema occurred.

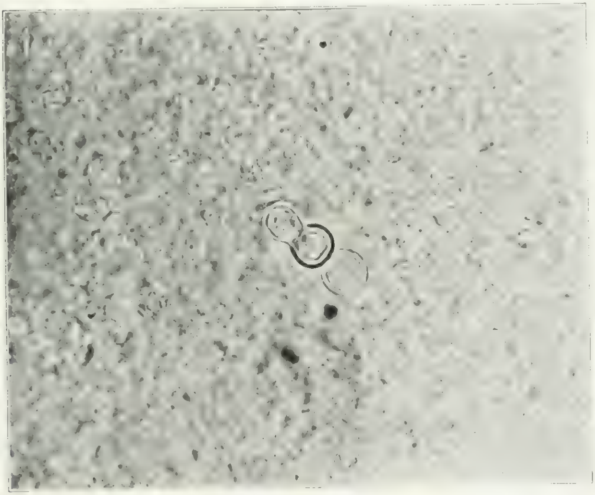

Fig. 25.—Round and budding forms of blastomycetes in sputum. Specimen mounted in 20 per cent. solution of sodium hydroxid. (Negative by Dr. W. A. Pusey.)

Albumin and casts occurred in the urine, and blastomycetes, having origin in abscesses of the prostate, were found in the urinary sediment in two cases of this series.

Pain was a constant factor in connection with the abscess formations, especially those involving the bones. This was caused by the pressure of the enclosed pus, and relieved by incision and drainage. The pain and tenderness in the affected joints at the onset were not so marked as in articular rheumatism, and not nearly so severe as would be expected with such extensive destruction as usually occurs later in the disease. Insomnia because of the pain was a prominent feature, and without doubt caused the marked irritability and melancholia of some patients.

Lesions of the spinal cord were responsible for paralysis of the lower extremities, and the involuntary discharge of urine and feces in two cases. No symptoms were produced by the lesions in the cerebrum, but this could hardly be expected from their size or location. One patient (Case 7) in whom a larger cerebellar abscess was found died during a convulsion, and signs of meningitis were manifested in one instance (Case 27). Marked neuralgic pain and gradual loss of vision, due to blastomycosis of the eye, were among the first symptoms noted in Case 20. The infection was located in the posterior chamber, and caused adhesions of the iris, irregularity of the pupil, opacity of the cornea, and marked congestion of the conjunctiva with purulent discharges.

The blood showed a reduction in the number of red blood-corpuscles and the hemoglobin percentage that would be expected in a secondary anemia of such a chronic infection. A leukocytosis is usually present, in some cases running as high as 30,000 per cubic millimeter. The average number of leukocytes in the reported counts, excepting a few in which the influence of sepsis distorted the blood-picture, was 16,800 per cubic millimeter. The average differential count was as follows: polymorphonuclears, 73 per cent.; small mononuclears, 17 per cent.; large mononuclears, 6.3 per cent.; transitionals, 0.7 per cent.; eosinophils, 1.5 per cent.; basophils, 0.1 per cent.; myelocytes, 1.4 per cent. In one case the myelocytes constituted 8 per cent. The mononuclear elements are relatively increased. This was more pronounced in those cases in which leukocytosis was less marked, as for example, one of the lowest counts (9,500 per cubic millimeter) showed only 55 per cent. polymorphonuclears.

The essential factor in the diagnosis of this disease is the demonstration of the blastomycetes in the sputum or in the pus of various lesions. This can usually be done so easily that there would seem to be no excuse for not recognizing the disease when it exists.

It should be remembered, however, that the organisms are easily overlooked in stained preparations, and the examination of fresh material is not a common routine measure. It happens, therefore, that the organisms in most cases have been found only when sought for, and when the nature of the disease has been suggested by its clinical or pathological features.

Blastomycosis should be ruled out in all cases of chronic pustular or ulcerative lesions of the skin, wasting pulmonary diseases, spontaneous superficial or deep abscesses, especially when connected with the bones, suppurative arthritis and suspected Pott's disease.

DIFFERENTIAL DIAGNOSIS

The conditions with which blastomycosis has most often been confounded and the important differential points will be briefly enumerated.

Coccidioidal Granuloma.—This disease has been ably discussed in the articles by L. Hektoen[1] and O. S. Ormsby.[2] That the disease from a clinical and pathological point of view closely resembles blastomycosis is generally conceded. The principal differential points advanced by the various authors are that in coccidioidal granuloma the nodular lesions resemble more closely those of tuberculosis, there is a greater tendency to involvement of the lymph-nodes, the cutaneous lesions are more ulcerative, the average duration of the disease is shorter than in blastomycosis, and reproduction of the organism in the tissues occurs principally by endosporulation.

Epithelioma.—The cutaneous lesions in Case 19 and also in other cases were first regarded as epithelioma, but close observation should readily differentiate these conditions. The principal points are the slower growth of epithelioma, the greater induration—extending into the tissues beyond the ulcer margin, and the absence of the bluish-red halo surrounding the border, which contains the characteristic miliary abscesses, and in which the blastomycotic organisms are usually found.

Tuberculosis.—Reference has already been made to the close resemblance between blastomycosis and tuberculosis, both clinically and pathologically. So far as the symptoms of the pulmonary infection are concerned, the clinical pictures of the two diseases are so similar that differential diagnosis is extremely difficult. Tuberculosis is the more destructive of the two, and cavity formation and marked hemoptysis are therefore more common. The examination of the sputum in most cases, of course, gives positive evidence of the condition present, and blastomycetes should be looked for in those cases of suspected tuberculosis in which the tubercle bacilli are persistently absent.

The affections of the bones are also very similar. The small bones and joints are perhaps more often affected in blastomycosis, the lesions are more often multiple, and associated pulmonary, cutaneous and subcutaneous lesions are more common. It should be noted that in several cases the blastomycotic ulcerations of the skin were mistaken for lupus. A very interesting and important point emphasized in Case 23 was the marked simulation of Pott's disease by the blastomycotic lesion of the spine. If any differences exist it might be stated that blastomycosis is more painful and rapid, and may begin by extension from the pleurae or adjacent structures rather than in the bodies of the vertebrae.

The tuberculin reaction was tried in several of the cases in this series, with negative results.

Syphilis.—Some of the pustules and ulcerations might be mistaken for syphilitic lesions and the hard indurated character, with subsequent softening of the deep abscesses, is suggestive of gummata. Roentgenograms of the affected bones have shown osteoporosis and periosteal thickening almost identical to that produced in syphilis, and one might be further mistaken and misled by the improvement which follows the administration of potassium iodid.

Inasmuch as positive diagnosis of obscure cases of syphilis are now being made with the Wassermann serum test, and it being realized that this is a group reaction, it was deemed of interest to try the reaction with blastomycosis. The serum in two cases was tested by Dr. F. G. Harris. One proved negative and the other was positive. It was assumed that the latter patient was at one time affected with syphilis, although no history could be obtained. The blastomycetic vaccine reaction may prove to be a positive factor in the diagnosis of blastomycosis. In three cases of blastomycosis in which cutaneous lesions were present, a distinct inflammatory reaction was observed in the local lesions after the injection of the blastomycetic vaccine filtrate. In the two cases which were not so far advanced a rise of temperature was obtained in from six to twenty-four hours after injection, the temperature in some instances persisting for two or three days. Such a rise in temperature did not occur in two cases of syphilis, three cases of tuberculosis and three normal persons who were subjected to the test.

Cutaneous tests consisting of the application of the filtrate and also triturated cultures in lanolin to scarified areas provoked no reaction sufficiently distinct to be considered specific. Ophthalmic tests with the filtrate were also negative. Different results might have been obtained with the use of cultures killed with less heat or in some other manner inasmuch as the ones used were subjected to a temperature of 110 C. (230 F.).

Dr. Boughton, using suspensions prepared by Dr. L. Hektoen, noted the formation of small nodules at the site of puncture and inoculation after the method of von Pirquet. These did not occur in a subsequent test. Other cutaneous and ophthalmic tests with these suspensions were negative.

PROGNOSIS

Experience to date indicates that the prognosis is extremely grave, the mortality thus far constituting nearly 90 per cent. It should be remembered, however, that in the majority of the cases the diagnosis was not established until the patients were in an extreme condition, and in several instances at necropsy. The recovery in three cases (Cases 2, 13 and 24), the remarkable temporary improvement and the evidence of healed lesions in the lungs at necropsy in Case 21, and the healed and healing lesions of the lungs, pleura, peribronchial lymph-nodes and bones in Case 23 of this series, would indicate that the infection can be overcome by the system, and that with early diagnosis and proper treatment the mortality can be much reduced. An important point to be remembered in connection with the prognosis given regarding local lesions is that live blastomycetes may persist for some time in the tissues of apparently healed regions of infection and again become active when treatment is discontinued or the patient's vitality reduced.

The duration of the illness has varied from four months to two and a half years. More than half the patients were sick for a period longer than one year. In many of the cases death was due to secondary pyogenic infection.

TREATMENT

Prophylaxis.—If the previously mentioned theory of infection should prove to be true, prophylaxis could be rather easily established. Pulmonary infection arising from the inhalation of mold spores could be prevented by the proper ventilation, lighting and drainage of residences and shops, thus preventing the dampness and moisture, which favor mold growth. Cutaneous infection could also be avoided by the careful cleansing of wounds received in the presence of decaying or moldy wood or other vegetable material.

Medical.—The influence of food, climate and hygienic measures is undoubtedly as beneficial here as in any other chronic infection. The recovery and cure in Case 13 was ascribed to climatic influence. Of specific medication, potassium iodid in large doses seems to have the greatest effect. It has been used successfully in a number of cutaneous infections, and was given credit for the cure in Case 2. It was also administered for a time in Cases 13 and 24, mentioned before as cured, and in Cases 21 and 23, in which an improvement at least of the pulmonary condition was manifested. (The internal administration of copper sulphate seemed to be of no benefit.) For the cough, pain and insomnia, codein is especially valuable, although in a few instances morphin was necessary. While medical treatment proved of benefit for the pulmonary infection, its influence on the metastatic lesions was not so marked, and these appear to be the cause of death in a number of instances. In the histological examination of the bone and subcutaneous abscesses, one is impressed with the fact that the extension and increase in size of the infected areas is often directly due to the pressure of the growing fungi, and surgical interference would therefore be indicated to a greater extent than has been employed. Clinically, excision of the cutaneous lesion has been very successful, and the relief of tension pain was always obtained by aspiration or drainage of the abscesses. In a few cases healing of abscesses was affected by this alone. Curettement of the bone abscess in Case 23 resulted in prompt healing, although reinfection occurred several months later.

Solutions of copper sulphate and iodin were applied to the ulcers, but with indifferent results, probably for the reason that the solutions do not penetrate to a sufficient depth to reach the organisms. Much better results were noted when these solutions were employed for irrigation of the abscesses. The Roentgen rays have proved very beneficial in the treatment of the cutaneous lesions, but they were not used to any extent in the cases of this series.

VACCINE THERAPY

Vaccination with blastomycetes and their products for therapeutic purposes was performed in three cases, two systemic cases (Cases 24 and 26) of this series, and one case of cutaneous infection (Fig. 40). The latter was in the service of Dr. O. S. Ormsby, through whose courtesy the treatment was instituted.

The material used consisted of the filtrate and the suspension of the triturated membranes of bouillon cultures grown at room temperature for periods varying from two to six months. The cultures were killed by heat (110 C.) and preserved with 0.8 per cent. chloretone. Subcutaneous injection of either the filtrate or suspension produced an area of induration varying in size according to the quantity used. A few of the larger areas became soft and fluctuating, owing to the formation of pus, which was sterile in all instances examined. Such indurations and abscesses were more constant and pronounced when the suspension was used, and did not occur with small quantities of the filtrate. A certain amount of pain was noted the first few days at the site of injection.

The general effect of such injections was usually a rise in temperature of from one-half to two degrees.[38] This became apparent in from six to twenty-four hours and sometimes persisted seventy-two hours or longer. With the rise of temperature occurred a feeling of general malaise and pain in the back and extremities. Pain, however, was more especially manifest in and about the local lesions, in which a distinct inflammatory reaction occurred, consisting of pain, swelling, increased discharge, and often bleeding from the ulcerated surface. This receded in from twelve to forty-eight hours. The crusts became detached, the ulcers decreased in size and general improvement followed. Deep abscesses approached the surface and ruptured, and healing of old fistulas occurred. These effects were quite as apparent from small amounts of the filtrates as from larger amounts of the emulsions. The latter produced more general disturbance and temperature; in fact, a rise of temperature was noticed in three cases not blastomycotic in which sterile abscesses followed the injection of 4 c.c. of the emulsion.

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[38] Figure 4, article by Boughton and Stober, this issue.

The reactions mentioned above occurred most typically in Case 24, in which improvement began with the first injection, and was continuous. After four months the patient felt well and strong, and of twenty-four lesions which were present at the beginning of the treatment. only two remained and these were in an advanced stage of healing. Two months later, however, one of these again became active and a new cutaneous ulcer appeared. Vaccinations were again resumed with the result that the lesions again are practically healed.

In Case 26, however, such good results were not obtained. The patient was in such poor condition when treatment was instituted that a different outcome could hardly have been expected. On July 10 an injection of 1.2 c.c. vaccine filtrate was followed by pain in the chest and a severe cough, lasting for two days. No increase of temperature or local reaction occurred. Six days later an injection of 1 c.c. of the filtrate produced a rise in temperature of 1.8 F., but no pain occurred in the local lesions or in the chest. On July 22 an injection of the same amount provoked only a slight rise in temperature, but a decided reaction in the superficial lesions was noted. Slight burning and itching were felt by the patient during the night, and the next day the margins of the ulcers became soft and the crusts dropped off. Apparent healing occurred for a few days, when the general condition of the patient became much worse. Cultures from pus aspirated from the various abscesses at this time showed no blastomycetic growths, but many staphylococci and a few streptococci were present. There were, however, a few blastomycetes found in the sputum, and it is interesting to note that nearly all were contained in giant-cells, a condition which was not previously observed.

On August 8, 2 c.c. of the filtrate were given, with very little success, and 3.5 c.c. on August 21 produced no reaction whatever. Dur-

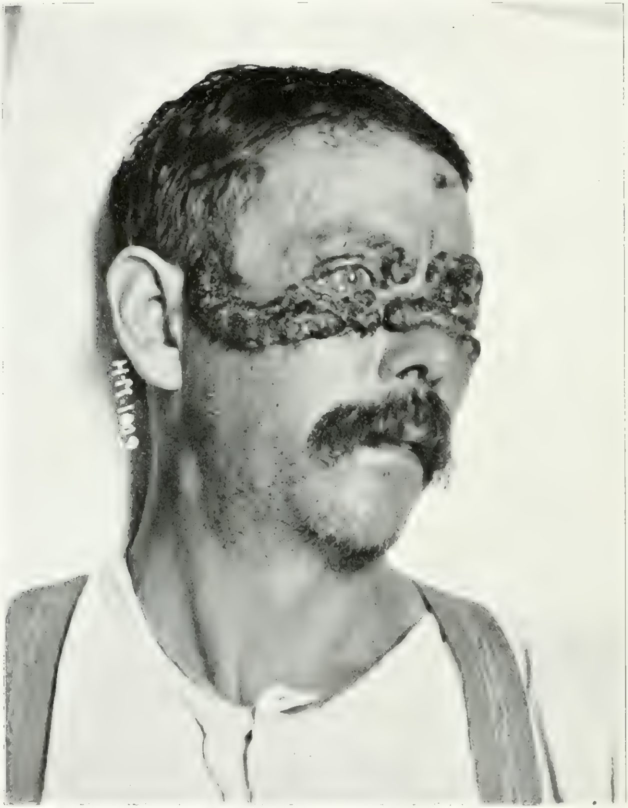

Fig. 26.—Case of cutaneous blastomycosis in which vaccines were used. (Courtesy of O. S. Ormsby.)

ing this time the patient had been gradually failing, and death occurred six days later.

The case of cutaneous blastomycosis (Fig. 26) was under treatment for two months, and at first some startling results were obtained. These, however, were only temporary. The patient was very anemic when he entered the hospital, the hemoglobin, estimated by the Dare instrument, amounting to 28 per cent. This was reduced by the repeated hemorrhages until only 12 per cent. was present. At this time the patient was unconscious and very weak. An arm-to-arm transfusion from a convalescing blastomycotic patient by Dr. Schroeder was followed by a rise to 27 per cent. and such an improvement in the patient's condition that consciousness returned, the dyspnea disappeared and he was able to sit up and partake of his food the following day. After a weak, however, he again became worse and died two days later.

From a most conservative point of view, the limited experience with this method of treatment is very encouraging and suggests that the injection of the filtrate of old blastomycetic cultures may not only be useful in diagnosis, but also prove to be a valuable therapeutic measure.

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†Since this article was completed a summary of the literature, together with a case report by Dr. Harter, has been brought to our attention. The bibliography of the work is most complete, especially the references to foreign literature.

A CASE OF SYSTEMIC BLASTOMYCOSIS*

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CASE XIX (1).[1]—*History.*—M. L., aged 42, married, a native of Poland and laborer by occupation, had lived in the United States four years. He was admitted to the Cook County Hospital April 8, 1907, to the service of Dr. Loeb with the diagnosis of acute articular rheumatism, because of the obvious swelling of the hand and foot.

After admittance to the ward, the following history was obtained with the aid of an interpreter: About four months before admission he was taken with a severe cold, cough and expectoration. This interfered but little with his general health. He next noticed a pain in the back, at first felt only on motion, later when lying on the back. A month later a swelling appeared at this painful area in the thoracic region, at the left of the median line. The cough, which persisted from the onset, became more marked, with abundant expectoration. His appetite began to fail and he noticed that he was losing weight. About four weeks before admission blood was present in the sputum for several days; the general weakness became so pronounced that he was compelled to stop work six weeks after the onset. Two months before admission painful swellings developed successively on the back of the left hand and foot and in the chest wall on the left side over the eleventh rib. The next lesion appeared three weeks before admission as a small papule on the right ala of the nose. This was quite painful and developed slowly into a warty growth. A week later enlargement of the submaxillary lymph-nodes on both sides of the neck was noticed. He complained of cough, profuse expectoration, night sweats, marked general weakness, and pain in the affected parts. He denied previous illness of either a general or specific nature. The family history was unimportant, except that his first wife died of tuberculosis. Three children born by his second wife are healthy. The patient had been a coal-heaver the past four years, and his habits were good.

Examination.—The patient was a middle-aged man, considerably emaciated, and very anemic. He lay on the right side and suffered with much pain on even slight movements involving the affected parts. The skin was moist, and perspiration especially profuse on the forehead and in the axillae. The respiration was free and rapid, averaging thirty per minute. The pulse was full and regular, the temperature 99.8 F., the scalp normal, the face drawn, the cheeks sunken, and the eyes partly closed. The pupils were dilated, equal and reacted to light and accommodation. There was no nystagmus or evidence of ocular paralysis. In the middle of the forehead was a small papillomatous growth covered with a thin yellow crust. On removal of this crust a small quantity of pus appeared. The margin was indurated red and sharply demarcated from the surrounding skin. At the margin of the right ala of the nose was another larger growth, 1.5 cm. in length. The papillomatous character was more distinct: it extended into the nostril for a distance of 0.5 cm., and was associated with considerable swelling of the adjacent tissues. The left ala of the nose was red, swollen and indurated, but the overlying skin was smooth. All these areas were very tender. The nasal cavity, mouth and pharynx were much congested with marked formation of mucus. No growths were visible, and the tonsils were not enlarged. The tongue was dry, the dorsum covered with a brown coat, the margins bright red. The teeth were in poor condition, many showing marked decay. In the submaxillary region on both sides of the neck was a hard, round, deep-seated swelling about the size of a walnut. The anterior and posterior cervical lymph-nodes presented a slight enlargement. No cervical rigidity was present. The thyroid was small and irregular. The bony framework of the chest was prominent, owing to the marked emaciation. Over the sixth rib on the left side in the nipple line was a rounded swelling about 2 inches in diameter. The overlying skin was red and adherent to the mass, and slight fluctuation was present. Posteriorly, on the right side over the twelfth rib, was another swelling of the same size, but the skin was not adherent and it did not fluctuate. Directly over the spine extending from the level of the eighth thoracic to the first lumbar vertebrae, and measuring 3 inches transversely, was still another swelling fluctuating and adherent to the overlying skin. Pressure over these areas excited marked pain.

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* Reported in part in Jour. Am. Med. Assn., 1908, I, 184.

1. Roman numerals in this and the following articles refer to number given in bibliography according to publication or occurrence. Arabic numerals refer to number in this series.

Expansion of the chest was slightly retarded on the right side. On percussion the lungs showed no changes anteriorly. Posteriorly, dulness was obtained over the lower lobe of the left side, and over a small area below the angle of the scapula on the right side. On auscultation of the lungs anteriorly a few bubbling râles were heard. On the left side over the upper part of the area of dulness the same signs were present, and whispered and voice sounds increased in intensity. At the base these râles were audible, but the breath sounds were suppressed.

The heart was slightly enlarged to the left. The apex beat was palpable in the fifth interspace in the nipple line. A slight murmur could be heard over the apex, but it was not transmitted to the left; other sounds were normal.

The abdomen was scaphoid. On percussion and palpation no abnormalities were noted. The liver and spleen were not palpable. The genitalia were normal. The lymph-nodes of the inguinal region were enlarged, forming a continuous chain on each side. On the dorsal surface of the right forearm were two small papillomatous growths, which resembled closely the one on the forehead. Considerable pain was elicited by deep pressure on the muscles of the forearm, but no swellings could be detected.

The left hand and foot were diffusely swollen, especially on the dorsal surfaces. The middle finger also showed a diffuse enlargement, being nearly twice as large as normal. These swellings were characterized by pain, fluctuation, tenderness and slight redness of the overlying skin. Examination of the nervous system revealed nothing abnormal.

Diagnosis, Treatment and Course.—The patient's condition aroused considerable interest and was diagnosed syphilis, pyemia and tuberculosis by different observers, the growth on the nose being generally regarded as epithelioma. Inasmuch as the diagnosis of syphilis was regarded as the most probable, the patient was given potassium iodid, 20 grains, and the protiodid of mercury, 1/5 grain, four times daily, with the effect of marked softening of the swellings. The potassium iodid was continued for a number of weeks, after which quinin and acetylsalicyclic acid were administered.

On April 19 the character of the nasal growth was recognized and a diagnosis of generalized blastomycosis was made. Blastomycetes were then demonstrated in smears of pus from the nasal growth. The organisms were also found in the sputum, urine sediment, and the aspirated contents of the swellings of the left hand and foot. The nasal growth was then excised and sectioned in celloidin. Microscopic examination showed changes typical of those described as occurring in blastomycosis of the skin. The epidermal layer presented a hyperplastic thickening with marked irregularity of the papillae. Scattered throughout were numerous intra-epithelial abscesses densely packed with lymphocytes, desquamated epithelial cells and polymorphonuclear cells, the latter predominating. Blastomycetes were present as round or oval refractile bodies, singly or in clumps, and budding forms were present. No giant-cells were present in the purely intra-epithelial abscesses, but they were quite numerous in the cutis. Here the cellular infiltration was dense, and, except in a few areas, the mononuclear cells predominated. Many plasma-cells and eosinophils were present. In several places the blastomycetes were found in the giant-cells. Attempts to isolate the blastomycetes in pure culture resulted in failure, because of the numerous other organisms present.

Blood-cultures at this time yielded the organisms, 5 c.c. of blood from the median vein being distributed equally into ten large test-tubes, each containing 10 c.c. of ordinary bouillon. After incubation for three days, two discrete white colonies were observed in one of the tubes, suspended in the fibrin meshes which permeated the fluid. These grew rapidly and began to show a distinct radiating structure. From one of these a smaller colony gradually separated by its own weight and was later removed for examination and subculture, to which reference will be made later.[2] The removal of this colony, which showed a distinct blastomycotic structure, resulted in the dissemination of organisms in the bouillon, for in a few days about thirty secondary colonies were observed scattered through the medium. By this time the original colonies had attained a diameter of 5 mm., the margins showing a fluffy radiating structure, while the center was becoming clear and indistinct. Pure cultures were easily obtained from the abscesses.

April 24 the red blood-cells numbered 2,420,000 per cubic millimeter, the white cells 14,200. A differential count of 200 cells showed polymorphonuclear neutrophils 67 per cent.; large mononuclear leukocytes, 9 per cent.; small mononuclear leukocytes, 16 per cent.; eosinophils, 2 per cent.; myelocytes, 3 per cent., and transitional forms, 2 per cent. May 8, the white cells numbered 22,800 per cubic millimeter. Still another examination on May 16 gave a red-cell count of 2,280,000 per cubic millimeter. The hemoglobin was estimated at 70 per cent. (Tallqvist). The leukocytes numbered 29,800. A differential count showed 77 per cent. polymorphonuclear neutrophils; 7 per cent. large mononuclears; 6 per cent. small mononuclears; 1 per cent. eosinophils, and 8 per cent. myelocytes.

On April 4 the urine possessed the following features: color, amber; specific gravity, 1.015. No sugar or albumin present. Diazo reaction negative. The sediment contained a few leukocytes. No red blood-cells or casts were present. An examination on April 25 gave about the same results, except that the sediment contained a few hyalin casts and leukocytes, and a large number of round and oval refractile bodies possessing a double contour and staining poorly with methylene blue. On May 6 there was little change, except that the specific gravity was high, being 1.028. A careful study of the refractile bodies found in the sediment left no doubt as to their character, as they did not dissolve in a 40 per cent. solution of potassium hydroxid, and presented numerous budding forms. They undoubtedly came from the pus from the abscesses in the prostate which were found at necropsy.

The sputum, which was abundant, was of a yellowish purulent character, with varying amounts of blood, which at times were sufficient to give it a brick-red or chocolate color. It was thick, but not tenacious. Repeated examinations failed to demonstrate tubercle bacilli in it. Many blastomycetes were found in the potassium hydroxid preparations. Nothing of importance was found in several examinations of the feces.

The patient became gradually worse and was helpless and bedridden after May 18. He complained bitterly of pain in the affected parts, especially on motion, or when the abscess walls became tense from pressure of the enclosed pus. Evacuation of these gave marked relief.

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[2] This is the second case in which the organisms have been recovered from the blood, the first instance having been recorded by Buschke.

The appetite continued fair, but in spite of this, he continued to lose flesh until the emaciation became pronounced. No nausea or vomiting occurred at any time. The bowels were fairly regular. Urination was normal. His sleep was often disturbed by the pain occasioned by involuntary movements about the bed. Perspiration was profuse and constant. His mental condition was very good, but became irritable and morose toward the end. The cough was not especially marked at any time, but the expectoration was profuse. The local lesions progressed more or less rapidly. The induration about the nasal lesion excised April 19 extended into the nostril for some distance, and it is probable that not all of the infected tissue was removed, as the wound again took on a papillomatous appearance. The opposite ala became red and swollen, and the surface covered with a thin brown crust. The abscesses on the hand and foot became soft and were aspirated April 19. Marked relief from pain resulted for a few days, but it became necessary to incise and drain a few days later. The pus obtained was thick, and varied in color from a light yellow to a dark brown. The abscesses on the back also were aspirated and the one on the left side of the chest incised May 15.

During this time new abscesses formed in the right forearm and hand and in the inner part of the left thigh. These were subsequently opened and pus of a similar nature evacuated. With one exception, the discharge from these abscesses had been continuous and profuse, and a distinct moldy growth occurred on some of the dressings in which the discharge had become dried.

There was a morning elevation of temperature, with marked evening remission, the latter often subnormal, at one time as low as 96 F. The high points ranged between 100 and 102 F. until the last two weeks, when temperatures between 102 and 103.8 were recorded. The pulse continued fairly steady between 100 and 120 per minute until two weeks before the patient's death, when it began to follow the temperature curve, going as high as 140. During the last four days of his illness it varied between 120 and 160, the temperature being subnormal. The respirations averaged about 26 per minute, and did not show any marked variations until the last week, when they also became more rapid. During the last four days they were rapid and labored, from 54 to 60 per minute until the end. Death occurred June 14 from exhaustion.

Necropsy.—Permission for a necropsy was secured three days after death and the following anatomic diagnosis made: miliary and nodular blastomycosis of the lungs, kidneys, spleen, cerebrum, pleura and lymph-nodes. Multiple blastomycotic abscesses of the cerebrum, cerebellum, prostrate, pleura, skin, osseous, muscular and subcutaneous tissues. Parenchymatous nephritis. Fatty changes, adenoma and angioma of the liver. Adenoma of the thyroid. General lymphatic hyperplasia. Shaven beard appearance of Peyer's patches. Atrophy of the testicles. Fibrous pleuritis.

The body was that of a middle-aged man 177 cm. (5 feet 10 inches) in length, and extremely emaciated. Considerable post-mortem lividity and some edema of the feet and ankles were present. The surface of the body was marked by a number of fistulas and elevated swellings, from 2 to 8 cm. (4/5 to 3 inches) in diameter and of three general types: a distinct papillomatous growth with a raised surface occasionally covered by a thin brown crust, the margins indurated and surrounded by an areola of discoloration. The second, excavated areas from 1 to 3 cm. (2/5 to 1 inch) deep, with granular friable bases exuding a thin serum. A third variety were lesions covered by thick brown rupia-like crusts removed with difficulty and resting on a bed of yellow pus. The bases of the ulcers thus formed were much more granular than those of the second variety. The last two varieties seemed to involve the subcutaneous tissues to a greater extent and suggested these as the point of origin. These lesions were distributed in the skin over the right upper lip, right eyebrow, knee, elbow and costal margin, the left cheek and on both alae of the nose.

The fistulas were either open and discharging a thin yellow pus or were covered by a brown crust. They were located on the inner side of the left foot, dorsal surface of the right hand and radial sides of both forearms. All were the results of operation, none of the abscesses having ruptured spontaneously. The subcutaneous abscesses varied in size from 1 to 6 inches in diameter, and were soft in consistency and distinctly fluctuating. The overlying skin was pale usually, freely movable over the swelling, and an edema of the adjacent soft parts was noticeable. On incision a variable amount of thick pus escaped from a bright yellow to a reddish brown in color, according to the amount of blood present. The walls of the abscess cavities were smooth and thin. Some were confined to the subcutaneous tissue and others communicated with cavities in muscle or bone. Those confined more or less to the subcutaneous tissues were located as follows: on the left side over the eleventh and twelfth ribs, one measuring 5 cm. (2 inches) in diameter. It lay just underneath the skin, to which it was adherent. Another of about the same size was present at a point on the right of the spine opposite the fourth and fifth thoracic vertebrae. Below this, directly over the spine, from the sixth thoracic to the third lumbar vertebrae, and extending to either side a distance of 6 cm., was a large fluctuating abscess. It contained a large quantity of pus and extended deeply into the muscles, exposing the seventh and eleventh ribs, and the ninth, tenth, eleventh and twelfth thoracic and the first lumbar vertebrae, the spine of the ninth thoracic being almost completely eroded, the others showing only slight involvement. The muscles in the neighborhood had undergone pressure atrophy. About an inch below this and to the left of the median line was another large fluctuating abscess 9 cm. (3½ inches) in diameter.

The abscesses in the muscular tissues seemed to be located between the muscles, separating them from each other and adjacent structures. Some of these, by extension, were subcutaneous. The walls of all were thin and smooth with a noticeable absence of ragged necrotic tissue. After removal of the pus and cleaning some of the cavities it was almost impossible to locate the boundary. In the submaxillary region was an abscess lying beneath the platysma and sternomastoid muscles. It extended 6 cm. (2⅓ inches) traversely and 4 cm. (1½ inches) in a vertical direction. Posteriorly, the great vessels of the neck were exposed. Another 20 cm. (8 inches) in length and 6 cm. (2⅓ inches) transversely was contained between the muscles of the thigh. Its floor was formed by the muscles, semitendinosus and semimembranosus, separating the gracilis and the biceps. The wall was made up of recognizable surrounding structures, and it was covered by fascia and skin. No communication with the bone existed. In the right forearm on the radial side was a large swelling extending from the wrist to within 3 inches of the elbow, an abscess between the extensor communis digitorum and skin, and the extensor carpi radialis brevis. It had no distinct wall or communication with the bone.

The abscesses involving bones were either confined to them or communicated with collections of pus in the adjacent soft parts.

The sinuses on the dorsal surfaces of both hands led into small abscess cavities between the tendons and bones of the hands communicating with diffuse infiltration of the deep palmar tissues. In the left hand, one-half of the shaft of the third and fourth metacarpal bones alone remained. Slight erosion of the adjacent superior surface of the os magnum and the unciform was present. On the middle of the left foot was a large abscess communicating with a cavity in the body of the internal cuneiform. An incision into the right ankle revealed a diffuse infiltration of pus in the tissues about the joint with erosion of the internal melleolus. The right knee-joint contained turbid fluid, and the synovial membrane was finely granular.

Directly over the sternum was an abscess 2 inches in diameter which communicated through a small opening with an abscess in the bone. This cavity measured ¾ inch in diameter and extended to the periosteum on the posterior surface (Fig. 1).

The seventh rib on the right side about the middle of the shaft contained an abscess 2 cm. (¾ inch) in diameter, communicating through a small opening in the periosteum on the internal surface with another collection of pus between the layers of the pleura. This rib when split down the center to the costal end appeared normal to within an inch anterior to the abscess (Fig. 2). From this point to almost the costal end the marrow was yellow. The cancellous bone was softer than normal and the spaces were filled with a purulent material, which, on examination, showed many blastomycetes singly and in clumps.

The deep cervical lymph-nodes were enlarged and fused, forming continuous masses on either side, about 3 inches long, and an inch in diameter. The majority were firm and light yellow. On section small yellow nodular elevations 3 mm. (⅛ inch) in diameter were seen. Others were softer and contained calcareous masses. The inguinal lymph-nodes were also enlarged, the largest on the left side measuring 1 cm. (½ inch) in diameter. The submaxillary, superficial cervical and axillary lymph-nodes were also somewhat enlarged, but did not show the nodules or softening. Both pleural cavities were obliterated by fibrous adhesions, and the lungs were removed with difficulty.

The left lung weighed 1,340 gm. (about 3 pounds). The pleura was thin and was covered with numerous fibrous tags. A number of miliary nodules could be seen and felt beneath its surface. The lung was firm, did not collapse and crepitated feebly throughout. On section, the cut surface was grayish-black and diffusely infiltrated with small white or gray nodules from 1 to 4 mm. (1/25 to 3/16 inch) in diameter. The intervening pulmonary tissue seemed normal and on pressure exuded a clear, frothy fluid. Sections from the posterior portions where the nodules were confluent floated low in water. Except for a small area, 1 cm. (½ inch) in diameter, in the center of the lower lobe, no softening was present. Considerable purulent mucus could be expressed from the bronchi, and in this a number of blastomycetes, some of which were budding, were found.

The right pleural layers were united into a white fibrous coat most pronounced on the lower part of the lung, where it measured several millimeters in thickness. Between its layers over the lower lobe and communicating with an opening in the periosteum of the seventh rib was the collection of pus already mentioned, occupying an irregular space measuring approximately 6 by 4 cm. (2¼ by 1½ inch.)

The right lung weighed 1,900 gm. (4 pounds 3 ounces). It did not collapse and crepitated throughout. On section (Fig. 3) its appearance was very similar to that of the left lung, except that in the lower lobe the nodules were more confluent and formed irregular grayish-white solid regions 1 cm. (½ inch) or more in diameter. No softening was present. In the upper part of the lower lobe there was considerable fibrous tissue about the larger bronchi.

The larynx, trachea and bronchi contained a large amount of frothy, purulent mucus. The mucous membrane was smooth. The peribronchial lymph-nodes were enlarged and firm. On section they were black and contained a few yellow regions from 1 to 3 mm. (1/25 to ⅛ in.) in diameter. Others with no coal pigment were softer in consistency, translucent, and grayish-red on section.

The thyroid weighed 40 gm. (1½ ounce). The left lobe was much larger than the right. Little normal thyroid tissue was present, the entire gland being made up of numerous round encapsulated regions from 0.5 to 2 cm. (3/16 to ¾ inch) in diameter, on section from gray to light brown.

The pericardial cavity contained about 4 ounces of yellow fluid. Its layers were normal. The heart weighed 200 gm. (7 ounces) and presented no gross changes. The aorta had a few puckered areas of thickening in the arch. The

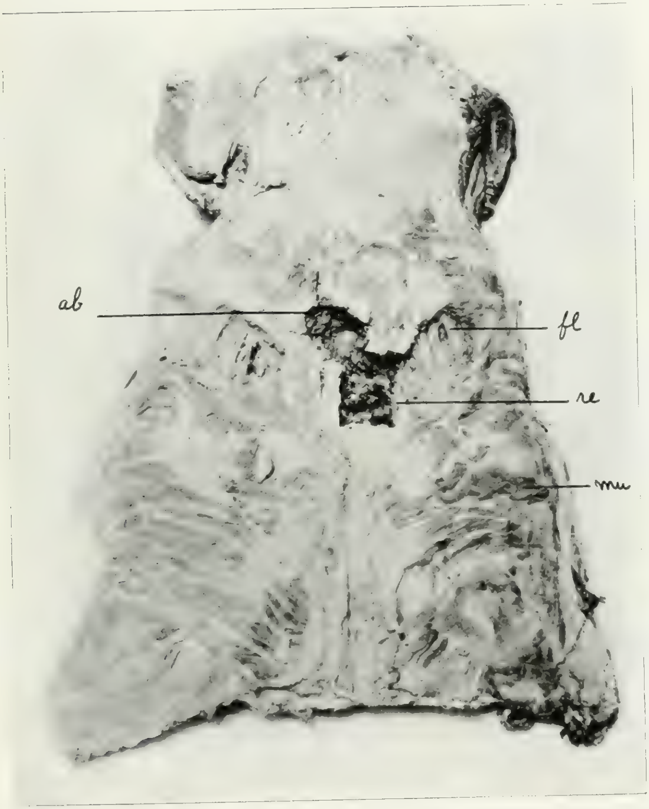

Fig. 1.—Blastomycotic abscess of the sternum: *mu*, pectoralis muscle; *ab*, the opening into an abscess in the gladiolus, the extension of which can be seen in that area where a rectangular portion (*rc*) has been cut away. This lesion communicated with a large subcutaneous abscess the floor (*fl*) of which can be seen.

periaortic lymph-nodes were enlarged and grayish-red, and contained small yellow nodules.

The pharynx and esophagus were normal. The tonsils were small and had large crypts containing a small amount of mucopus. The peritoneal cavity contained a small amount of clear fluid. The peritoneum was smooth. Fibrous adhesions were present between the liver and colon, about the appendix and about the posterior margin of the spleen. The omentum was devoid of fat. A considerable degree of gastro-enteroptosis was present.

The stomach and pancreas showed only post-mortem changes, the intestines the shaven-beard appearance of Peyer's patches.

The gall-bladder and ducts were normal.

The liver weighed 1,900 gm. (4 pounds 3 ounces). The right lobe was enlarged and bore the imprint of the ribs. The surface was smooth, yellow and mottled with red. The centers of the lobules were dark-red, the peripheries light yellow. In sections an angioma, 1.5 cm. (⅝ inch) in diameter, and a small adenoma were found, but no nodules or abscesses were discovered.

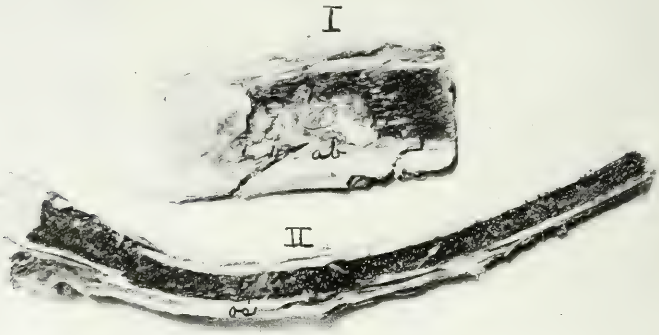

Fig. 2.—I, blastomycotic abscess (*ab*) of rib, part of which has been cut away. Subcutaneous abscesses secondary to lesions of the ribs have been common features in most of the cases. II, section of a rib showing blastomycotic osteomyelitis most marked at *os*. The blood of this patient contained many myelocytes.

The spleen weighed 100 gm. (3½ ounces). The capsule was somewhat thickened, the consistency firm. On section the tissue was pale and the trabeculae and lymphoid tissue seemed increased. Numerous blastomycetes were obtained from a few small yellow areas, 1 mm. (1/25 inch) in diameter.

The kidneys together weighed 400 gm. (14 ounces). On section of the left kidney the cortex measuring 8 mm. (⅓ inch) rolled out beneath the capsule; the pyramids, from 16 to 18 mm. (2/5 in.) in length, were dark. The capsule stripped readily, leaving a smooth surface. Beneath the capsule in the substance of the kidney were small yellow nodules from 1 to 2 mm. (1/25 to 1 12 inch) in diameter, quite solid and easily separated from the tissue. When one of these was crushed under a cover-glass in a 20 per cent. solution of sodium hydroxid, a number of blastomycetes were found. The right kidney corresponded to the left, except that the nodules described were more numerous, twelve being counted on the cut surface and beneath the capsule. The ureters were normal.

The adrenals were normal except for a few small yellow nodules which were saved for histological examination. The bladder was small, the walls thickened and the trabeculae prominent. The mucosa of the neck of the bladder and the posterior urethra were reddened, and on pressure yellow pus escaped from the ducts.

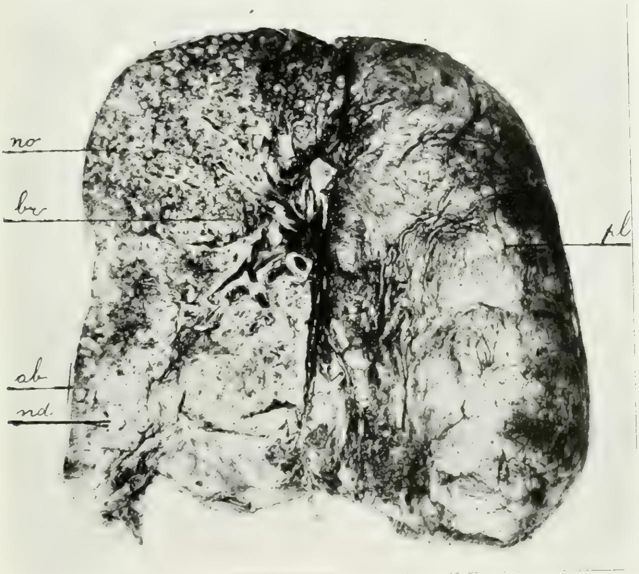

Fig. 3.—The right lung showing the thickened pleura (*pl*) and numerous nodes (*nd*) and nodules (*no*) on the cut surface. A small abscess (*ab*) was present between the pleural layers, and considerable fibrosis existed about the larger bronchi (*br*).

The prostate was enlarged and contained a fluctuating region in the left lobe. On section this lobe presented a central necrotic mass, with lines of the same material, or fine white nodules radiating to the capsule. The right lobe contained a few small abscesses. The seminal vesicles were distended with clear brown fluid. The testicles were atrophic, the vasa deferentia normal.

The brain weighed 1,400 gm. (3 pounds, 1½ ounces). No gross lesions were present externally. On section, in the cortex on the left side, near the middle of the sulcus between the parietal and occipital lobes, a small abscess 2 mm.

(1/12 inch) was exposed. Blastomycetes were demonstrated in the pus in this abscess. In the right hemisphere a small nodule was found in the temporal lobe, one in the parietal lobe and two in the occipital lobe. These were small, located in the cortex and usually at the margin of the white matter. In the right lobe of the cerebellum there was also a small nodule, and a second occurred in the left lobe as a white nodular mass with central degeneration from 1 to 4 mm. (1/25 to 1/6 inch) in diameter: this second lesion extended from near its internal surface to within ½ inch of the extreme lateral margin. Blastomycetes were also demonstrated in the necrotic material from this area. The spinal cord externally and on section presented no gross changes.

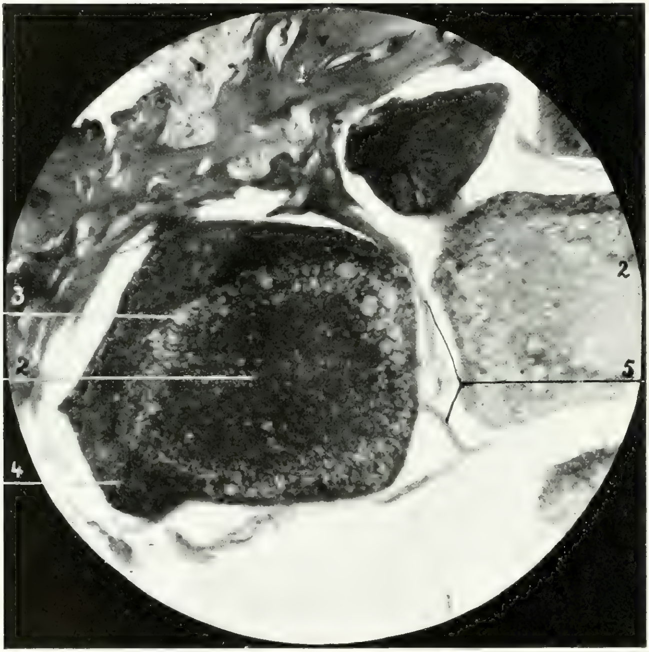

Fig. 4.—Section of the sternum showing infection of the bone marrow: 1, bone; 2, central zone of necrosis; 3, light areas representing clumps of blastomycetes; 4, peripheral border of unaffected marrow; 5, bony partitions which are sometimes absorbed, allowing the infected areas to become confluent, thus forming an abscess.

The histological examination failed to reveal any lesions characteristic of blastomycosis in the liver, adrenal testes or vasa deferentia. In the lungs there were found all degrees of coalescence of focal lesions, some so minute that they were little more than single alveoli, others large districts with more or less necrosis of their centers. As a rule they possessed the feature of blastomycotic nodular lesions elsewhere in the character of the cellular exudate, giant-cells, organisms, etc. The fungi were very abundant. In the thickened pleura covering the right lung the so-called "miliary abscesses" were compressed and flattened out between the layers of fibrous tissue. In the spleen isolated organisms, some of them budding, were occasionally found in the sinuses at points where there was as yet no sign of tissue reaction, at other places minute focal lesions had developed about them. Many of the subcutaneous abscesses possessed no enveloping granulation tissue; especially was this true when the wall was formed by striped muscle. In the corium the inflammatory reaction was much more pronounced, and evidences of pressure were abundant. In some sections the fungi in the corium were so numerous as to resemble roughly fat areas with the high powers of the microscope.

The lesions in the brain were peculiar in the abundant necrosis, the appearance of bands of fibrous tissue between adjacent lesions probably due to pressure, and also in the angular bizarre giant-cells, which were relatively few. The lining of the right knee-joint was converted into granulation tissue resembling in a general way the margins of all large lesions; organisms were present but not numerous. The bone lesions differed perhaps most markedly from all the others in the comparatively little reaction of the tissue, necrosis being the predominant change (Fig. 4). In the prostate the change seemed confined to the glands which in the regions involved were more or less destroyed and converted into abscesses containing many organisms.

Bacteriologic Examination.—In addition to the cultures obtained during life, material was taken at necropsy from the knee-joint and the abscesses of the spleen, pleura and prostate. Pure cultures were obtained from the first three mentioned and a mixed culture from the prostate. The organisms were demonstrated in smears of material taken from the nodules of the kidney and the abscesses in the brain and rib. All the cultures obtained from pus and necrotic material appeared to be similar, but that obtained from the blood showed a few differences. A detailed comparative study of these is included with that of other organisms in the general summary.

A CASE OF SYSTEMIC BLASTOMYCOSIS

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CHICAGO

CASE XX (2).—*History.*—J. S., aged 39, a Polish laborer, was admitted May 14, 1907, to the service of Dr. Heinick with the following history: The patient states that his present trouble began three months ago with severe pain in the right half of the head and face, most marked, however, over the malar prominence. This continued without remission until a month ago, at which time he began to experience pain in the right hip and knee. The latter became much swollen, and so painful that walking or standing was prevented.

A week later, pain was felt in the anterior part of the chest and in both shoulders, especially on inspiration or movements of the shoulders. Two weeks ago the left wrist became tender and swollen. A slight cough, present since the onset, has been more marked during the last two months, with blood occasionally in the sputum. The power of sight in the right eye gradually diminished, and at present the patient cannot recognize small objects a few feet distant. Although the appetite remained good he lost about 20 pounds. He also states that previous to this illness he had been strong and healthy. He is married and has five children. Venereal infection is denied. For the past four years he was engaged in the scrubbing and dusting of Pullman cars.

Examination.—The following points were noted in the examination: The patient is of medium stature, extremely emaciated and appears to suffer much pain even on slight movement. Beneath the scalp, over the vertex of the skull, is a tender fluctuating mass an inch in diameter. The conjunctiva of the right eye is red and edematous. Dulness is obtained by percussion over the upper lobe of the right lung anteriorly, and over the angle of the scapula posteriorly. On auscultation tubular breath-sounds and bronchophony are heard over the apex in front, but no râles are present. Over this dull area posteriorly the breath and voice sounds are diminished, but a few subcrepitant râles can be heard. The left lung appears to be normal. The heart is rapid but no changes can be demonstrated. Nothing of importance was found in connection with the abdomen or its viscera.

The right hip, knee and sternoclavicular joints are red, swollen and painful on motion. Fluctuation can be obtained over the knee. The right great toe is also swollen, and contains an abscess which has ruptured, discharging thick blood-stained pus. Scattered rather symmetrically over the body are fourteen deep and subcutaneous abscesses, varying in size from 1 to 5 cm. in diameter. These are distributed as follows: three in each arm, two over the chest and abdomen and six in the lower extremities. There are also pustular cutaneous lesions distributed on the right side of the nose, right cheek, left arm and both legs.

The temperature on admission was 101 F. The subsequent course of the disease was characterized by morning remissions of temperature to 98 or 99 F., and evening elevations to 101 or 102, associated with profuse sweats. This continued until the last week of illness, when the temperature became irregular and did not register much over 100 F. until the day of the patient's death, June 20. The pulse varied between 90 and 120 beats per minute until the last ten days, when it continued quite regularly between 120 and 140 per minute. The respirations averaged 26 per minute, becoming somewhat more rapid during the height of the fever. On June 15 a sudden change in the patient's condition was noted, the respirations becoming labored, rising to 60 per minute. He became cyanotic and complained of pain in the cardiac region, and for the next five days the respiration ranged between 44 and 56.

Up to this time the patient had manifested but few symptoms. Cough was of rare occurrence, and expectoration was so scanty that material for examination was obtained with difficulty. No organisms were found in that examined, but they were present in the mucus removed from the larynx at the necropsy. No tubercle bacilli were found. The abscesses increased in size and number, and were associated with great pain, especially on motion. A number of these were incised, and thick bloody pus was evacuated.

Diagnosis, Treatment and Course.—The diagnosis of blastomycosis was established June 10 by the demonstration of blastomycetes in the pus and their growth on culture mediums. Prior to this the patient was given a preparation of iron, quinin and strychnin as a tonic, and morphin, 1/4 grain, from one to four times a day for the pain. On June 17, three days before death, he was given potassium iodid, 15 grains, and copper sulphate, 1/4 grain, three times a day, without, however, any beneficial effect.

The majority of the abscesses which were incised continued to discharge profusely, and in the pus of a few of these the organisms could not be found. A note relative to an examination made on June 17 of the condition of the eye is as follows: "The conjunctivae of both eyes are much congested, and a purulent discharge is present. The cornea of the right eye is opaque, the pupil dilated and irregular, and the iris clouded and adherent in its right lower quadrant. The vessels leading to this region are engorged. These results were corroborated by Dr. Brown Pusey.

Two crusted ulcers were present at this time over the left eyebrow, three about the right shoulder, two on the right knee, three on the left knee and two on the left buttock, in addition to the lesions described previously, which had since become ulcerated. A majority of these presented the papillomatous appearance characteristic of cutaneous blastomycosis. It was noted that the abscesses which were not opened increased in size, and the left knee was also much swollen, and fluctuation could be determined.

Both jugular veins were dilated, the left one measuring an inch in diameter, the right forming a globular mass over 2 inches in diameter. No pulsation could be determined, but the veins became much distended during inspiration. The area of cardiac dulness was not much enlarged. The heart sounds were obscured by the rapid respirations. The lungs presented an impaired resonance in front with dulness to flatness behind. On auscultation anteriorly the breath sounds were harsh in character and a few coarse râles could be heard at the apex. On the sides the breathing was tubular in character, becoming distant and indistinct posteriorly.

A number of attempts to obtain cultures from the blood were made without success, and an estimation of the leukocytes made early in the course showed no increase. No noteworthy changes in the urine were found. The patient died of exhaustion as previously stated, on June 20, four months after the illness began.

Post-Mortem Examination.—Through the courtesy of Dr. W. H. Hunter, coroner's physician, the following data were obtained: The body was extremely emaciated and presented the numerous cutaneous lesions and the superficial and deep abscesses previously described. The latter were very extensive and contained a thick yellow or brown pus. The walls were made of adjacent tissues, and no lining membrane could be observed, except in those cases in which the abscesses had been incised and secondary infection had taken place.

An abscess 2 inches in diameter was present beneath the scalp, on the left side at the vertex. It communicated with a region of softening in the parietal bone an inch in diameter involving almost its entire thickness. An irregular perforation, 8 mm. in diameter, existed in the inner table exposing the dura mater, the surface of which was rough and necrotic.

The first rib contained an abscess near its junction with the sternum. The bone here had been destroyed, and an opening in the periosteum communicated with a collection of pus beneath the bulging skin. Similar abscesses were present in the third, fifth and sixth ribs on the right side. The right knee-joint was much enlarged and its synovial cavity contained a large quantity of pus, the crucial ligaments were destroyed, and slight erosions existed at their points of attachment. The articular surfaces were otherwise smooth. The left knee also contained a large quantity of pus. The left elbow was much swollen. The olecranon had been fractured, and the head of the ulna was completely disorganized. An abscess extended from this point into the forearm along the ulna to the wrist. The terminal phalanx of the right great toe had been destroyed, and erosion with abscess formation in the small bones of the left wrist was present. Still another collection of pus was found over the sternum communicating with an abscess in the sternum. The latter occupied the greater portion of the right half of the manubrium, and extended to the periosteum of the posterior surface. On section the infected bone about the abscess was slightly yellow, and considerably softer than normal.

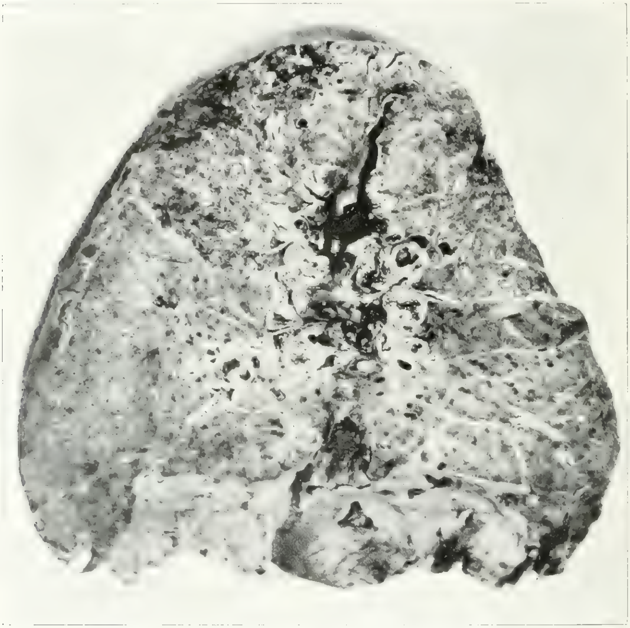

Fig. 1.—Right lung. The infection here was so extensive that the lung was almost solidified, and presented an appearance not unlike that of an organized pneumonia. Blastomycotic nodules can be seen with difficulty, but the organisms were very numerous in the microscopic sections.

The right eye showed the changes noted in the examination made a few days before death. The tonsils were enlarged and the crypts contained a caseous material in which no blastomycetes were found. The cervical, mediastinal and peribronchial lymph-nodes were enlarged.

Both pleural cavities were obliterated anteriorly by fibrous adhesions, which were especially firm at the apex (right) and opposite an abscess in the third rib. The tissues about the apex were so involved in the cicatrical mass that the right jugular vein was constricted. Above this point the vessel was dilated to the extent that its lumen measured 1½ inches in diameter. Posteriorly, on both sides, the chest contained a large amount of turbid fluid, and the pleurae were covered with a thin fibrinous exudate.

The right lung weighed 960 gm., was quite firm and did not collapse. Slight crepitation could be obtained over the greater portion. The posterior surface was covered with a thick coat of fibrin, and anteriorly fibrous tags were present. The interlobar fissures were obliterated. On section the upper lobe was firm, and dense white bands of connective tissue radiated from a cicatricial region torn from the third rib, to which it was adherent. The intervening tissue was quite solid and contained very little air. Numerous small white nodules were scattered throughout, and a few small caseous areas were present, the material from which contained many blastomycetes. The middle and lower lobes on section showed an increase of the interlobular connective tissue. The greater part of the lung was firm, smooth and translucent, with irregular intervening regions of apparently normal lung, from which a frothy fluid could be expressed. No air was present in the solid portions. Many small white nodules were scattered throughout the lung (Fig. 1). The left lung weighed 700 gm., and presented a small amount

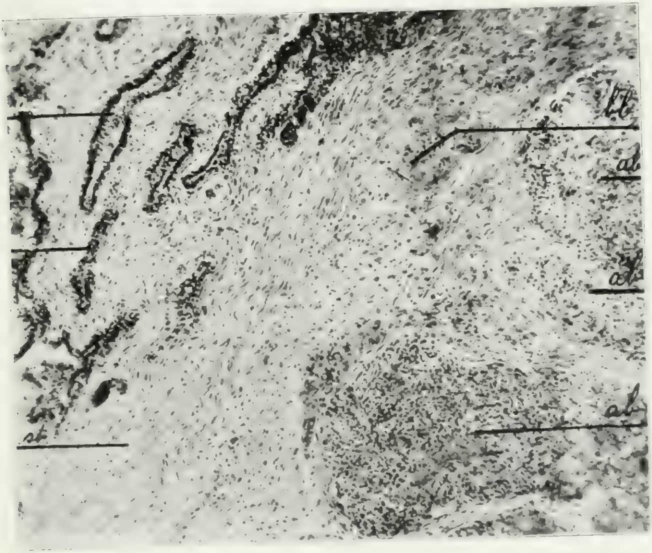

Fig. 2.—Photomicrograph of blastomycotic abscesses of the prostate gland: *ac*, normal acini; *ab*, abscesses in infected acini; *st*, fibrous stroma; *bl*, a small clump of blastomycetes.

of fibrin on its posterior surface. It crepitated feebly throughout, and on section the appearance was similar to that of the middle lobe of the right lung. The general appearance was that of an organized pneumonia. The small bronchi were filled with a thick purulent material in which blastomycetes were demonstrated. The pericardial cavity contained 3 ounces of turbid fluid, and the lining membrane was slightly roughened. There was a slight thickening of the mitral valves. No lesions were visible in numerous sections of the musculature.

The stomach and intestines possessed no changes of importance, except that Peyer's patches were pigmented and reticulated. The mesenteric lymph-nodes were considerably enlarged. The liver and kidneys were opaque and gray on cut surfaces. The spleen was normal. These viscera were carefully examined for blastomycotic lesions, and a number were found in the kidneys. The adrenals, bladder, testicles, pancreas, vas deferens and seminal vesicles were normal. The prostate was enlarged, and on section a small abscess 5 mm. in diameter was exposed in the lobe. The glandular structure of the left side showed slight changes.

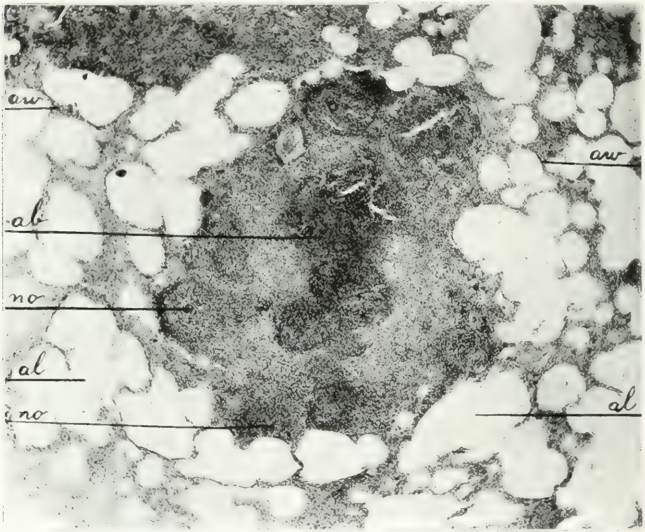

Fig. 3.—Photomicrograph of a fairly typical blastomycotic lesion of the lung: *ab*, necrotic center of a small node made up of *no*, confluent nodules; *al*, alveoli; *aw*, alveolar walls.

No nodules were found in the left lobe of the cerebrum, and the remainder of the brain was not obtained for examination.

Anatomical Diagnosis.—Serofibrinous pleuritis and pericarditis; miliary blastomycotic nodules of the lungs, pleurae and kidneys; multiple blastomycotic abscesses of the lungs and prostate and the osseous, muscular and subcutaneous tissues; blastomycotic ulcers of the skin; blastomycosis of the right eye;[1] purulent bronchitis; parenchymatous degeneration of the kidneys and liver; fibroid induration of the lungs; fibrous pleuritis.

Histologic Examination.—No changes of importance were found in the stomach, intestine, mesenteric or tracheobronchial lymph-nodes. The liver was moderately fatty; in sections of the spleen occasional isolated blastomycetes were found without changes in the surrounding tissues. In some of the kidney sections blastomycotic abscesses, the size of a low-power field (Obj. iii, Ocular ii, Leitz) occurred in the cortex and the usually rather abundant giant-cells containing organisms were scattered about the abscess margins. The heart-muscle cells were atrophied, and on the epicardium and beneath it the changes ordinarily present in slight fibrinous inflammations were found; nothing, however, was found to indicate the essentially blastomycotic nature of the pericarditis.[2]

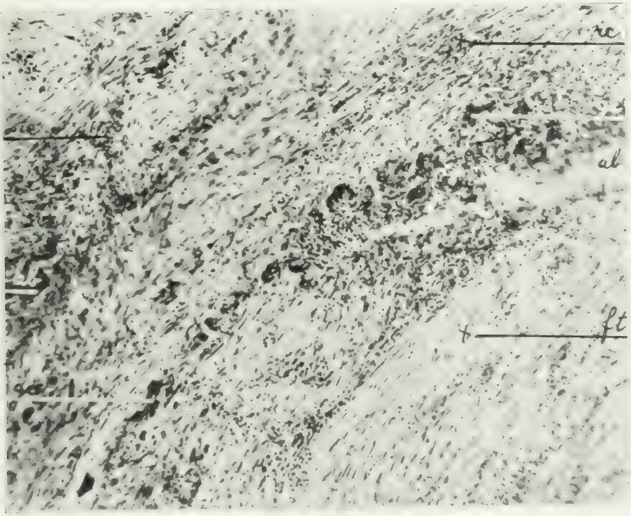

Fig. 4.—Photomicrograph of a section of thickened pleura: *ft*, fibrous tissue; *ab*, small abscess formations; *gc*, giant-cells; *rc*, areas of round-cell infiltration.

In sections from the sternum at some distance from the abscess, the changes were limited to the periosteum, which was thickened and under which were collections of partially necrotic leukocytes and many organisms. The marrow appeared but little altered.

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[1] Owing to the fact that the lesions of the right eye developed during the course of the illness, considerable speculation was aroused as to its nature. Unfortunately permission to remove the eye was not obtained. The eyeball was therefore rotated, a sterile puncture made and a portion of the vitreous humor removed. From this, a pure culture of blastomycetes was obtained. In view of this result the assumption that the lesion was one of metastatic blastomycosis is perhaps not far-fetched. Supporting this view are the facts that pain noted about the region of this eye and disturbance of vision, indicating its involvement, were among the first symptoms.

[2] See bacteriological examination.

In the sections of the cutaneous and subcutaneous lesions the changes in some were much like those described for chronic blastomycotic dermatitis, to which there were added the extensive regions of destruction produced by the deeper lying suppuration; in other sections the process was more limited to the subcutaneous tissues. Except for the presence of the focal lesions so characteristic of this disease, which were scattered about the subcutaneous abscesses, the inflammatory process possessed the features of almost any chronic suppuration.

In the prostate the great number of organisms filling some of the acini was indeed remarkable (Fig. 2). The glands seemed dilated by the organisms alone. From such accumulations accompanied by little alteration in the surrounding gland tissue there were all degrees of change for the extensive destruction noted in the gross examination. Focal lesions, the minute blastomycotic "abscesses" with their peripherally located giant-cells, were conspicuously absent in the prostate sections examined. The changes in the lungs (Fig. 3) varied in the different regions examined from recently produced bronchopneumonia to rather marked fibrosis. In both, as well as in the greatly thickened pleura, the "abscesses" were scattered about, although in the pleura these disseminated lesions with organisms were flattened out between the dense masses of fibrous tissue. (Fig. 4.)

Bacteriology.—Pure cultures of blastomycetes were obtained from the pus of various abscesses, from time to time during life. At the post-mortem examination, medium was inoculated or material taken for inoculation from the blood, bile, pleural, pericardial and peritoneal fluids, the vitreous humor of the right eye and pus from the knee-joint, and the abscesses of the neck and prostate gland.

Streptococci were grown from the blood, pleural and peritoneal fluids and the pus of the knee-joint. The blastomycetes were isolated culturally from the pericardial and pleural fluids, vitreous humor of the eye and the prostatic abscess. The results of study of these organisms are mentioned elsewhere in this report. The presence of the streptococci was regarded as the result of a terminal infection inasmuch as there were clinical manifestations of such a condition during the few days prior to the patient's death. The failure to recover any organisms culturally from the pus of the neck and the knee-joint would indicate possibly that with and without secondary infection the blastomycetes may die or disappear from the pus of the abscesses in which they had previously been demonstrated.

Thanks are hereby extended to Dr. Heinick, attending physician, for his permission to report the case.

A CASE OF SYSTEMIC BLASTOMYCOSIS

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CHICAGO

CASE XXI (3).—*History.*—M. C., Italian, aged 17, was admitted to the Cook County Hospital, May 20, 1907, to the service of Dr. Goodkind, with the following history: His illness began five months ago with the appearance on the anterior surface of the middle of the right thigh of an abscess which ruptured and discharged a thick, fetid, dark-brown pus. A papillomatous crust formed subsequently at the site of the abscess. There was at the same time a small abscess near this which healed in a few days. Two months later a sharp stabbing pain occurred in the right knee. Motion soon became restricted and in two weeks a swelling of the joint appeared. This gradually increased so that in two months the knee was twice its normal size. It remained in this condition until the time of his admission to the hospital. One month after the onset of the pain in the right knee, the left knee became similarly involved, but the pain and swelling were less severe. The right ankle also became affected, but the process did not progress and at present (the time of his admission) shows no signs of inflammation. Marked swelling, accompanied by pain and tenderness, occurred successively in the left ankle, both elbows, left wrist and the first metacarpophalangeal joint of the left hand. A small papule developed in the left eyebrow one month after the commencement of the joint troubles, and since then similar lesions have appeared on other parts of the face and head. (Fig. 1.)

The patient was born in Italy and from the age of 10 was engaged in hard manual labor on a farm. Four years ago he came to the United States and has worked at intervals as an organ-grinder and helper in a machine shop, until the onset of the present illness. He lived in the congested Italian district on the west side of Chicago, and his living quarters were unhygienic in the extreme. The rooms themselves were dry at the time of investigation (summer) but the basement in which the closets were located was wet, and decomposing feces and wood were found in many places. His health had always been good and he denied venereal infection. The family history was unimportant except that his father died two years ago after an illness of two months during which time he coughed frequently, often expectorating blood.

First Admittance to Hospital.—When admitted to the hospital, on account of the multiple arthritis, the diagnosis of chronic rheumatism was made. The course of the disease, however, during the subsequent two months, led to the consideration of tuberculosis and syphilis as possible explanations of the symptoms, and the latter was favored because of an interpretation given to the appearance of the bones of a roentgenogram of the hand. The subsequent development of an abscess beneath the scalp, and its characteristics resembling those encountered in other cases of blastomycosis, led to the examination of aspirated pus and the discovery of the organisms. The patient now was anemic and emaciated; seemed quite comfortable and complained of pain and stiffness of the joints. The pulse was 108; temperature 101.8 F.; respirations 28. On the face were a number of small oval, indurated, purplish ulcers, their edges being fairly regular and rounded margins sloping outward to the skin around them. The largest of these situated above the right eye and measured 6 by 20 mm. Other similar lesions in various stages of involution were present on the back of the neck, scalp, arms, thighs and left ankle. An oval "rice-paper" scar was present on the upper part of the right thigh, and below this a fistulous opening discharged bloody pus. It was surrounded by an oval area of indolent granulation tissue and represented the site of rupture of the first abscess which appeared. Beneath the scalp three small abscesses were found; one of these was more deeply situated and seemed to be connected with the bone.

The eyes, ears, nose and neck were normal. The chest was negative on inspection except over the tenth rib in the posterior axillary line on the left side, where there was a soft rounded swelling the size of a hazelnut, and evidently attached to the rib. Resonance was impaired over both apices in front and behind. The respiratory murmur was roughened and expiration prolonged. No râles were heard anywhere. Posteriorly below the left scapula, resonance was impaired and the voice and breath-sounds slightly diminished. A faint systolic murmur over the pulmonic area and a slight enlargement of the liver were the only alterations in the further examination of the chest, abdomen and genitalia.

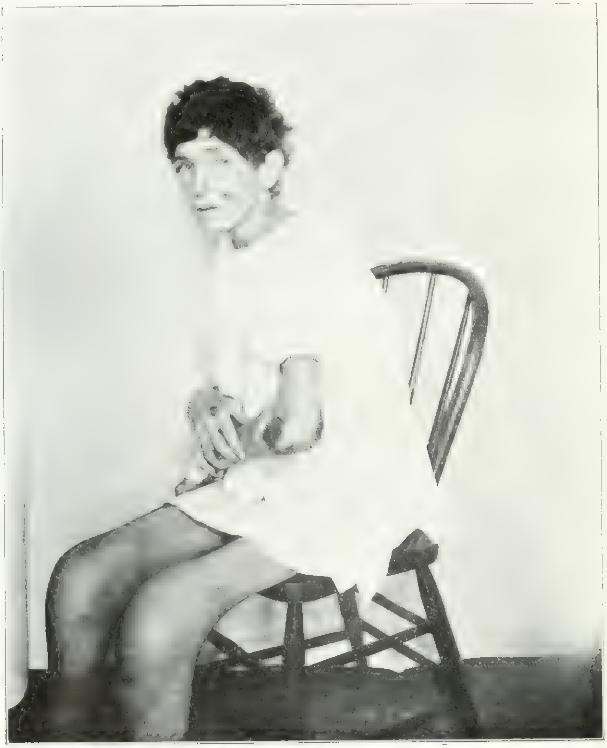


Fig. 1.—M. C., photographed a few days before death. Note the cutaneous lesions on the left cheek and right hand, the swollen and ulcerated condition of the left elbow, and the marked swelling of the knees.

The muscles of the extremities were atrophied. Both elbows, the right wrist, both knees and the left ankle were swollen and tender, and motion was restricted and painful. There were in the right hand two small abscesses involving the first metacarpophalangeal joint and the middle phalanx of the fourth finger. A sinus on the palmar surface of the fourth finger communicated with the last-named abscess and discharged a thick brown pus. The left wrist was tender, and extending from an abscess in the first metacarpophalangeal joint were two sinuses, one dorsal and one palmar, each discharging a thick yellow pus.

There were no disturbances referable to the nervous system. The superficial cervical and epitrochlear lymph-nodes were slightly enlarged.

The urine was amber, clear, acid in reaction, specific gravity 1.018, and contained no albumin, sugar or casts. No blastomycetes were found in the urine obtained after massage of the prostate. Examination of the feces failed to show anything of importance.

The blood contained 3,800,000 red cells per cubic millimeter; 9,600 white cells and 65 per cent. hemoglobin (von Fleischl). A stained specimen showed slight poikilocytosis but no nucleated red cells. The differential white count was as follows: polymorphonuclear neutrophils, 55 per cent.; small lymphocytes 32 per cent.; large lymphocytes, 11 per cent.; eosinophils 2 per cent. No cultures were obtained from the blood in several attempts.

The course of the disease was slow and marked by several remissions and exacerbations. The pulse ranged from 80 to 120; the temperature was highest in the evening and varied between 98 and 103.6 F. After June 22, when the diagnosis was established, the patient was given increasing doses of potassium iodid, tonics and fresh air treatment and rapidly improved. The pain in the joints disappeared and he left the hospital July 8 and resumed his occupation, organ-grinder.

Second Admittance to Hospital.—Ten days later he returned to the hospital with a marked aggravation of all his joint-symptoms. He coughed much, expectorating slight amounts of mucoid material, and suffered greatly from pain in the joints; the pulse was 84; temperature 100.8; respirations 24. The right ankle, which was normal previously, was swollen and tender, and two new abscesses had appeared on the ulnar side of the right wrist and on the tarsal surface of the left wrist extending into the hand.

The physical signs in the lungs were also more pronounced, but no râles were heard. Administration of potassium iodid was resumed with no improvement for about eight days. Many new abscesses appeared successively on the hands and feet, and the temperature ranged up to 103.4 F. Copper sulphate was now given internally in ¼ grain doses three times a day and the hands and feet, in which were many discharging abscesses, were dressed with hot 0.5 per cent. solution of copper sulphate. The patient again improved, the cough subsided; the abscesses healed and the joints became less painful.

Repeated examinations of the sputum were made for the tubercle bacillus and blastomycetes with negative results until August 5, when budding blastomycetes were found. The improvement continued and the patient gained in weight and strength. The temperature did not rise above 99 F. after August 11. All the fistulas closed and he left the hospital August 17 in good condition, there being only slight limitation of motion in the elbows and knees. At the time of discharge 150 grains of potassium iodid three times a day and ½ grain of copper sulphate three times a day were being given.

Third Admittance to Hospital.—The patient again applied for admission to the hospital Dec. 12, 1907, and was assigned to the service of Dr. Mix and afterward transferred to the surgical service of Dr. Ryerson. During the second furlough of four months he suffered many hardships. He had taken no medicine, and had tried to return to Italy, but the officials at New York refused him passage and he was forced to sell papers on the streets in order to obtain food. He entered the hospital much emaciated and in a very weak condition.

with an exacerbation of all his old lesions and some new ones. The pulse ranged from 90 to 130, temperature 98.6 to 103.6 F., respirations 22 to 30. There was a general adenopathy, especially noticeable in the axillary, cervical and inguinal regions. Large abscesses involving both knees, wrists, elbows and ankles were present, the one about the right knee being very large and fluctuating and extending half way up the thigh. The others had ruptured and discharged a thick yellow pus. He suffered excruciating pain on movement of any of these joints. The ulcers of the skin were larger, and new lesions were present on the lip and the back of the neck. Impaired resonance and harsh breathing obtained over the apices of both lungs.

Increasing doses of potassium iodid and a nutritious diet were again administered, but the patient became weaker despite treatment and died Jan. 16, 1908.

Early in the course of the disease, Bier's passive congestion treatment was used, but it seemed to do little good. As soon as the patient was able to leave his bed he spent nine hours a day in the sunshine and open air.

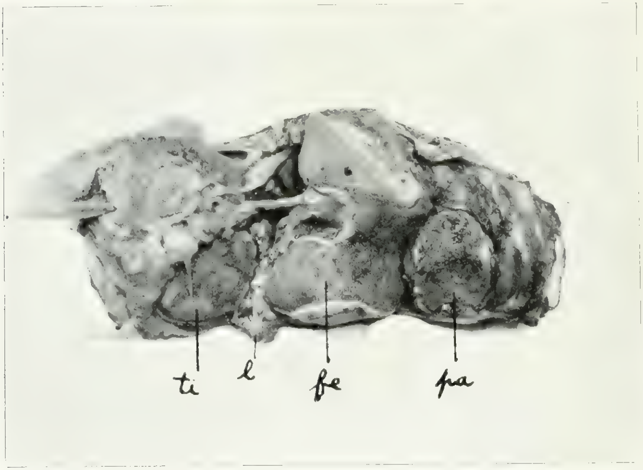


Fig. 2.—Articular surfaces of left knee: *ti*, eroded surface of head of tibia; *fe*, lower end of femur on which only a portion of the articular cartilage remains; *pa*, patella, in which are two abscesses, the openings of which are exposed; *l*, articular ligaments which were so disorganized that subluxation occurred.

Necropsy.—A post-mortem examination (Dr. Stober) was held two days after death and the following is the anatomical diagnosis: indurated blastomycotic bronchopneumonia of the left lung; blastomycosis of bones, subcutaneous and cutaneous tissues, pons Varioli, inguinal and axillary lymph-nodes; acute vegetative mitral endocarditis; fatty liver; parenchymatous degeneration of the kidneys; fibrous pleuritis; hyperplasia of the lymphoid tissue of the ileum; edema of the lungs; hydropericardium; atrophy of the heart, pancreas and testicles; emaciation and anemia.

The body is that of an extremely emaciated young man. Numerous cutaneous lesions, abscesses and fistulas are present, the majority of which have been described in the clinical report. Both knees are markedly swollen and the skin covering them contains several ulcers and discharging fistulas. A posterior subluxation has occurred in the right knee, and the same condition can be produced in the left knee. The joint-cavities contain a large amount of bloody pus, the periarticular tissues are disorganized, the ligaments destroyed and the cartilages have disappeared, exposing the rough granular surface of the bones (Fig. 2.) About these joints large communicating abscesses exist; the one above the left knee extends the whole length of the thigh and contains nearly a quart of pus. Another above the right knee is about half as large. Discharging abscesses involving the elbows and the small bones of the feet are also present. The articular structures of the latter have been practically destroyed. There are abscesses communicating with the lymph-nodes in both groins and in the right axilla. The lymph-nodes of the left axilla are enlarged and pink on section.

The pleural cavities contain about 2 ounces of a clear yellow fluid, with slight fibrous adhesions about the apices and also to the diaphragm on the left side. The pericardial cavity contains 4 ounces of a clear yellow fluid.

The lungs weigh 620 gm. Both crepitate freely and do not collapse. The left lung on section is mottled light gray and on pressure exudes a slight amount of frothy fluid. In the extreme lower margin of the lower lobe and externally is a region of induration roughly 5 by 1 cm. in diameter, somewhat circular in outline and directed toward the root of the lung, where it is continuous with a similarly indurated tissue behind the main bronchus, in which there are several yellow regions of necrosis (Fig. 3). The pleurae overlying the consolidated lung tissue next the diaphragm is thickened and binds the lung to that structure. The lung beneath contains numerous small blood-vessels and bronchi surrounded by firm tissue heavily pigmented with coal-dust. The pericardium is generally adherent to the left lung. The remainder of this lung as well as the right lung is unchanged. The tracheo-bronchial lymph-nodes contain large amounts of coal pigment and are slightly enlarged.

The tongue is normal. The tonsils are small and from their crypts a purulent material is expressed. The esophagus is smooth; the trachea and larynx are slightly hyperemic and contain mucopus.

The heart weighs 240 gm. The pulmonary tricuspid and aortic valves are normal. The mitral valve is thickened and on the edge of both cusps are fine warty vegetations the largest of which measures 1 mm. in height. The heart-muscle is pale; the left ventricle wall measures 5 mm. in thickness, the right 2 mm. The aorta and coronary vessels are normal. The liver weighs 1,400 gm. Its surface shows the imprint of the ribs. On section the tissue appears somewhat opaque and light yellow. The spleen weighs 200 gm. Its capsule is thickened, its consistency firm, the cut section brown, and there is an increase in the connective tissue. No microscopic nodules are present.

The brain weighs 1,600 gm. It is normal externally. In numerous sections, one blastomycotic nodule is found in the pons a few millimeters below the ventral surface.

The kidneys weigh 280 gm. On section the kidney substance bulges; it is a grayish-yellow; the cortex is increased in thickness and the capsule strips readily, leaving a smooth surface.

The testicles are small, and sections expose an increase in connective tissue. The bladder is small and contains a small amount of turbid urine. The rugae are fairly prominent; the posterior urethra is congested and slightly granular. The prostate and seminal vesicles are normal. The pancreas is firm and small. The mucous membrane of the stomach is thin, and small ecchymoses are present about the pyloric region. The intestines are normal.

The left leg was amputated through the thigh for a more detailed examination. A small opening into the knee-joint from an abscess in the internal condyle was found, as well as several small regions of softening in the cancellous bone of the patella. The abscess in the condyle was 3 cm. in diameter and the passage into the joint one-third as large. The bone about the abscess as well as that just beneath the articular cartilages of both tibia and femur was soft and diffusely yellow; on crushing a semipurulent fluid was obtained (Fig. 4). On the antero-internal surface of the tibia at the junction of the upper and middle thirds an opening 5 mm. in diameter was found passing through a raised bony and shell-like periosteum under which was a small abscess not connected with the marrow cavity. The epiphyses of the lower end of the tibia and fibula also contained small yellow softened regions communicating with abscesses over both malleoli which had ruptured externally (Fig. 5), the one over the external malleolus continuous with an abscess extending beneath the Achilles tendon. Occupying the greater part of the dorsum of the foot was a sharply demarcated region of necrosis, and the tissues bordering this were

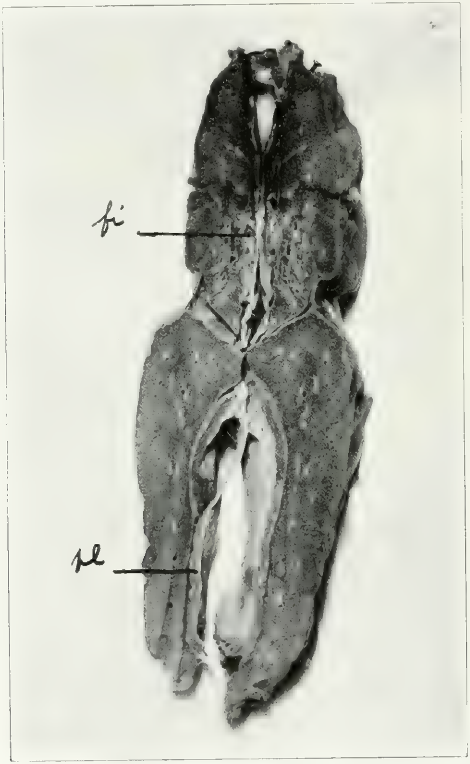


Fig. 3.—Section through the lower lobe of left lung: *fi*, fibroid area representing healing blastomycotic lesions; *pl*, thickened pleura adherent to the diaphragm.

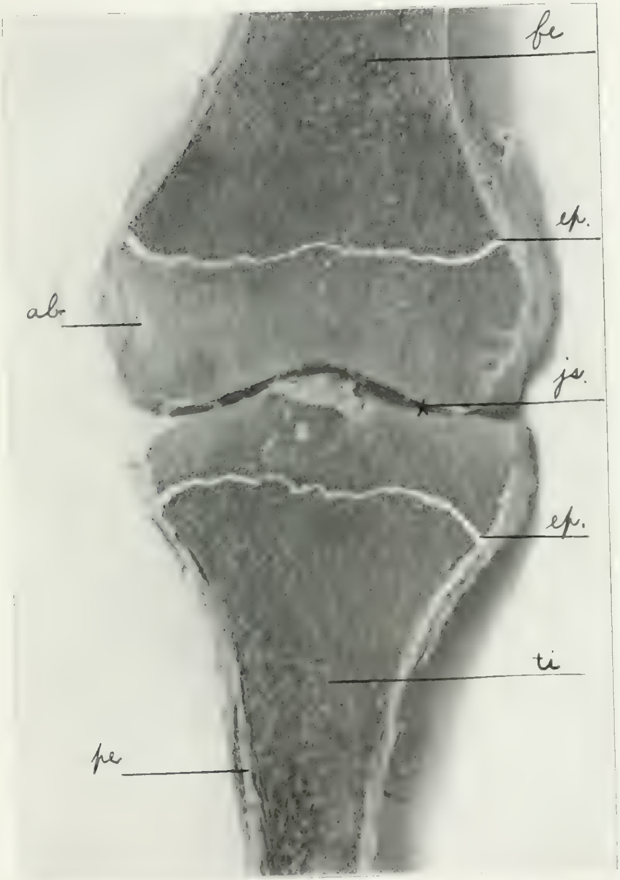


Fig. 4.—A longitudinal section of the left knee-joint: *fe*, lower end of femur; *ti*, upper end of tibia; *ep*, epiphyseal line; *js*, eroded joint surfaces; the light color of the adjacent bone represents the extent of the blastomycotic process; *pe*, healed periostitis; *ab*, abscess in epiphysis which communicated with the joint.

without evidence of reaction. In this region the unchanged extensor tendons lay bare, and beneath were the fragments resulting from the disorganization of several of the tarsal and portions of the metatarsal bones (Fig. 6). In the pus of the joint cavities, bone abscesses and adjacent soft cancellous marrow were to be found many round and budding blastomycetes, some of which possessed capsules of unusual thickness.

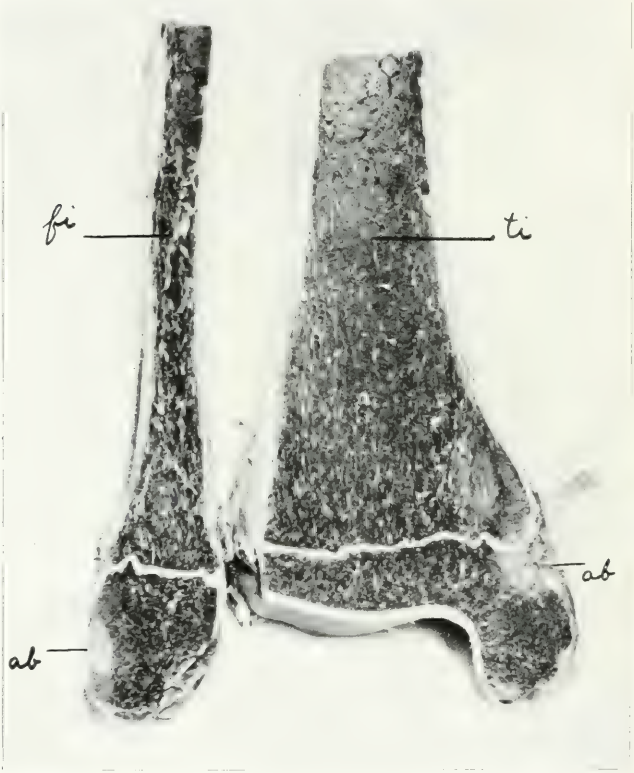


Fig. 5.—Longitudinal section through tibia (*ti*) and fibula (*fi*) with abscesses (*ab*) in the epiphyses.

Histology.—In sections of the indurated region in the left lung, compressed and distorted bronchi were found surrounded by masses of adventitious fibrous tissue; one of these bronchi contained enormous numbers of blastomycetes. Several of the minute so-called abscesses with organisms and the other features of such blastomycotic local lesions were scattered about in this fibrous tissue. The other alterations were those commonly encountered about regions of chronic disease in the lungs.

The changes in the bones were of special interest on account of the extensive necrosis. Sections were studied from the abscesses in the patella, fibula, femur and tibia, and the alterations were quite similar. The centers of small abscesses and the tissue near the surfaces of such as had discharged their contents were made up of disorganized and necrotic bone, leukocytes and red cells. In the sections from the yellow and soft cancellous bone beneath the articular cartilages

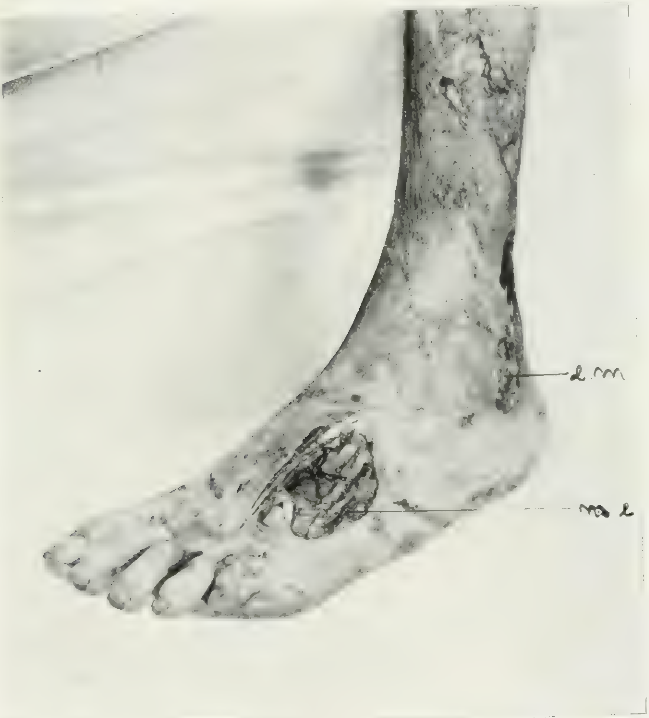


Fig. 6.—Ulcerations communicating with blastomycotic abscesses in the metatarsus (*me*) and external malleolus (*em*). Muscles, bones and tendons have been exposed.

there was a diffuse necrosis for the depth indicated in the gross description, a necrosis evidently due to the rather regular extension into the head of the bone of the blastomycosis of the joint. This diffuse necrosis was difficult to explain by the coalescence of local lesions. In some sections zones of mononuclear leukocytes surrounded the necrotic tissue, but no evidences of granulation tissue about these was found, and organisms occurred out-side the lesions in the cavities of the marrow where but little change had taken place. Histological changes in accord with the gross description, both indicating the formation of new bone from the cambium, were found in the shell-like but perforated and imperfect outer wall of the abscess on the inner surface of the upper part of the tibia.

In the inguinal lymph-nodes not only were focal lesions present, such as have been repeatedly described in the tracheobronchial lymph-nodes, but also peripheral lymph sinuses were found crowded with organisms, evidently in the current since the adjacent tissues were without alterations. In the spleen, too, organisms were found; at one point a clump of fifteen or twenty, at another, budding forms and about them no evidences of tissue reaction. The lesion of the pons, 3 mm. from the ventral surface and approximately 1.5 mm. in diameter, contained numerous organisms and was apparently formed by the coalescence of more minute local lesions. The changes in sections of other tissues and organs conformed to the anatomic diagnosis.

Bacteriology.—The *Staphylococcus albus* and *aureus* were recovered from the blood, pleural fluid, bile and pus from the abscesses of the knee-joints, left inguinal and right axillary regions. Blastomycetes were demonstrated in the pus of the abscesses mentioned as well as in the necrotic material from numerous bone lesions, but were not obtained in culture. The failure to cultivate these organisms from material yielding cultures during life is not an infrequent post-mortem occurrence.

This report is of more than ordinary interest on account of the improvement which occurred during the first two periods in the hospital, and also because of the existence of relatively slight blastomycosis in the lungs at the time of death — the organisms having disappeared from the sputum some time previously and coincidentally with the fewer evidences of pulmonary alteration on physical examination — and the very extensive involvement of the subcutaneous tissues, bones and joints.

A CASE OF SYSTEMIC BLASTOMYCOSIS

H. J. MYERS, M.D., AND A. M. STOBER, M.D.
CHICAGO

CASE XXII (4).—*History.*—The patient, C. T. S., entered the Cook County Hospital May 8, 1907, to the service of Dr. Ryerson. He complained at the time of dyspnea, pain in the right side of the chest, occasional night sweats, chills and fever. His right ankle was painful and swollen, and on the face and left side of the abdomen were cutaneous lesions which his physician had diagnosed and treated as lupus. The first of these to occur was a small papule over the eleventh rib on the left side, discovered accidentally in December, 1906, while scratching his body. This ulcerated and gradually increased in size until March, 1907, at which time it measured an inch in diameter, and was treated as lupus, without benefit. A similar lesion developed on the left side of the chin after the top of a small papule was cut off during shaving. A short time later another lesion occurred over the left eye, following the scratching of what the patient thought was an insect-bite. In January, 1907, he first noticed night sweats, and several months later a cough associated with bloody expectorations. In February he went to Arkansas, and while there suffered from chills and fever, which were relieved by quinin. At this time he also noticed a tenderness of the right external malleolus which later became painful and swollen, together with an abscess of the heel causing a gnawing pain at night and some soreness when the limb was first used in the morning.

The patient had been a clerk for three years. His previous illnesses were unimportant. His father died of gastric carcinoma at the age of 45. From May to November, 1906, he was engaged in dredging, during which time he slept in a cabin-boat, which he stated was quite damp at times. During June and July he slept with a man who was suffering from what he thought was consumption.

Examination.—At the time of admission the patient was poorly developed, considerably emaciated and very anemic. Crusted lesions were present above the left eye, on the left side of the chin and on the left side of the abdomen, and there were soft fluctuating abscesses on the left side of the neck and over the right external malleolus, the latter quite red and very painful on pressure. Examination of the lungs demonstrated dulness on percussion over the right upper lobe, increased transmission of whispered and spoken voice-sounds, and numerous small mucous râles. No dulness was obtained over the remainder of the right lung or over the left lung. Expiration, however, was prolonged, and the breath-sounds somewhat harsh in character. A few moist râles were heard over both bases. The heart action was strong and forcible, with accentuation of the aortic and pulmonary second sounds. The liver extended one finger's breadth below the costal arch; the spleen was not palpable. The urine was normal, save for an occasional hyaline cast. The temperature on the day after admission was 100 F.; pulse 76; respirations 22. On May 10 Dr. Ryerson made an incision into the swelling over the right external malleolus and considerable pus was evacuated. Extending through the periosteum to the epiphysis of the fibula a small sinus was found which from its appearance was considered tuberculous. It was enlarged, the cavity curetted, swabbed with tincture of iodin, and closed with a small drain. The abscess in the neck was also curetted and the region of supposed lupus on the side excised. The wounds closed by first intention, but infection in the external malleolus appeared several months later. On May 14, four days after the operation, a swelling appeared on the left side of the face and profuse night sweats occurred. Pain was felt in the right foot, especially at night, and a week later the patient experienced sharp, severe pain over the lower part of right chest; this was increased by inspiration and continued for four days. The next few days he complained bitterly of pain in both ankles and the right wrist, and Bier's passive hyperemia treatment was tried for some time without, however, producing much benefit. On June 7, a fluctuating swelling appeared in the right forearm, and the patient complained of pain in the back between the shoulders.

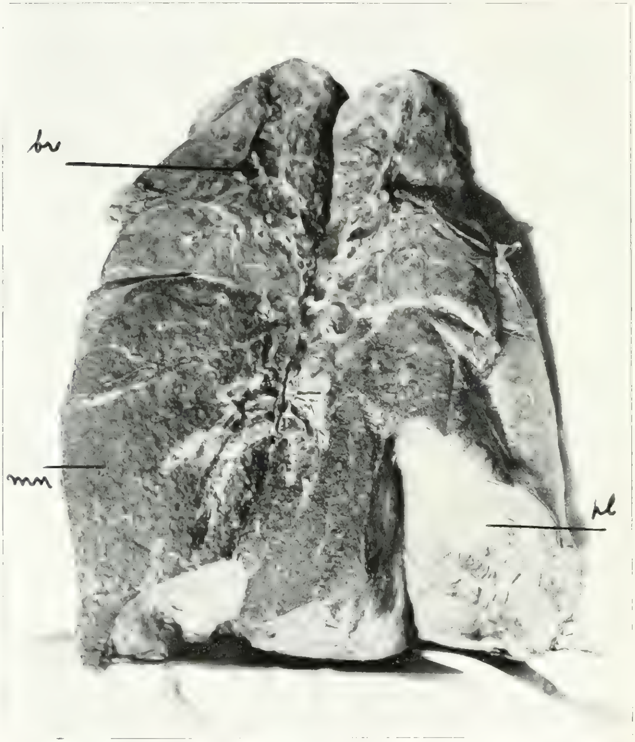


Fig. 1.—Right lung, Case 22; *br*, bronchiectatic cavity in upper lobe which has undergone fibrosis; *mn*, miliary blastomycotic nodules in lower lobe; *pl*, thickened pleura in which nodules were also present.

Treatment and Course.—Up to this time the disease had been considered to be generalized tuberculosis. Iron, quinin and strychnin had been administered as tonics, and other remedies as indicated for the pain and insomnia. Because a viscid bloody pus obtained on June 11 from an abscess over the left tibia possessed the characteristics of pus from the blastomycotic abscesses in other cases it was examined with the result that numerous blastomycetes were found. Subsequently these organisms were cultivated in pure culture from various abscesses. From this time potassium iodid, 60 grains, and mercurial inunctions, 1 dram, were given daily. A month later the mercury was discontinued and $\frac{1}{4}$ grain of copper sulphate was given three times a day. During the next two months the disease was marked by progressive weakness, emaciation and pain in the affected parts, especially in the knee- and ankle-joints. The pain was quite constant and so severe that large doses of codein and later of morphin were required for its relief. The temperature ranged quite regularly between 99 F. in the morning and 102 in the evening. Occasional sweats were noted. The pulse varied from 80 to 130 beats per minute, the respirations from 20 to 26. Toward the end the patient was quite irritable, and at times refused both food and medicine.

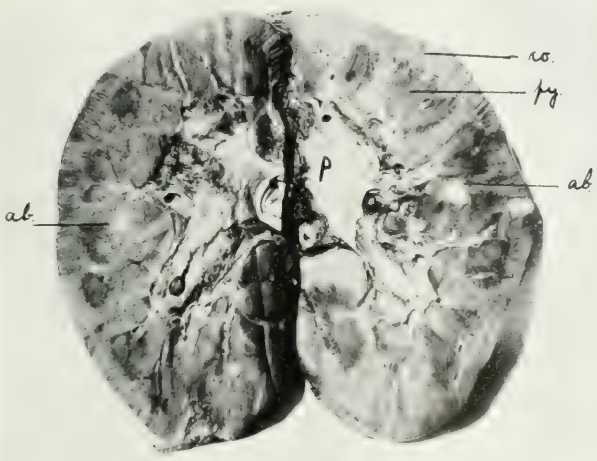


Fig. 2.—Right kidney, Case 22; *co*, cortex; *py*, pyramid; *P*, pelvis; *ab*, blastomycotic abscesses.

On September 14, three days before death, five typical ulcers were present on the face. Fistulas communicating with abscesses existed over the left mastoid, in both forearms, the left thumb, the inner part of the left thigh, in both knees, the tibiae, ankles and dorsal surfaces of the feet. Other abscesses were present over the vertex and the occiput, sternum, clavicle, sixth rib, knee, heel, ankle, inner side of thigh and middle of leg — all on the right side; on the left side other abscesses were present over the heel and external aspect of the leg. Two large confluent fluctuating regions extended from the seventh cervical to the first lumbar vertebrae. Both knees were swollen, fluctuating and tender. General adenopathy was present and emaciation extreme. The other alterations noted previously had changed but little. The patient became delirious a few days before death, which occurred Sept. 17, 1907.

Necropsy.—Permission for a post-mortem examination was obtained two days after death and the following conditions found: Anatomical Diagnosis: Healing and discharging blastomycotic abscesses and ulcers of the skin; blastomycotic abscesses of the bones and muscles; blastomycosis of the lungs, peribronchial lymph-nodes, liver, spleen, pancreas, kidneys, cerebrum and cerebellum; serofibrinous and fibrous pleuritis; parenchymatous nephritis; chronic splenitis; hyperplasia of the mesenteric lymph-nodes; pigmentation of Peyer's patches; fenestration of the Thebesian and aortic valves; patent foramen ovale; decubital ulcers; emaciation.

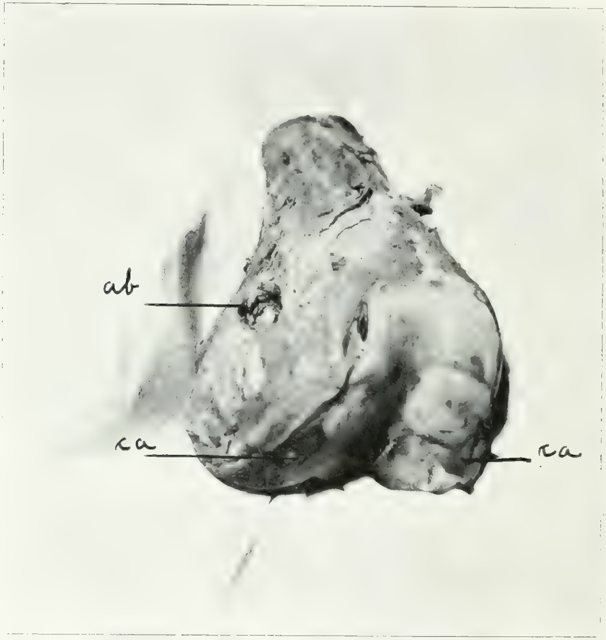


Fig. 3.—Lower end of femur which was involved in a suppurative arthritis: *ab*, abscess in epiphysis which communicated with the joint; *ca*, eroded articular cartilages.

Both pleural cavities were partially obliterated by fibrous adhesions and contained a considerable amount of slightly turbid fluid posteriorly. The pleural layers enclosing this fluid were covered by a thin deposit of fibrin. Beneath the pleurae of the lungs were a large number of miliary nodules feeling like shot. The left lung weighed 900 gm., did not collapse, crepitated throughout, and small nodules were felt in its substance. The pleura of the lower lobe possessed numerous fibrous and fibrinous tags. On section the lung was brownish-red and on pressure exuded a large amount of frothy red fluid. Many miliary nodules were disseminated throughout the lung. At the apex beneath the pleura (torn

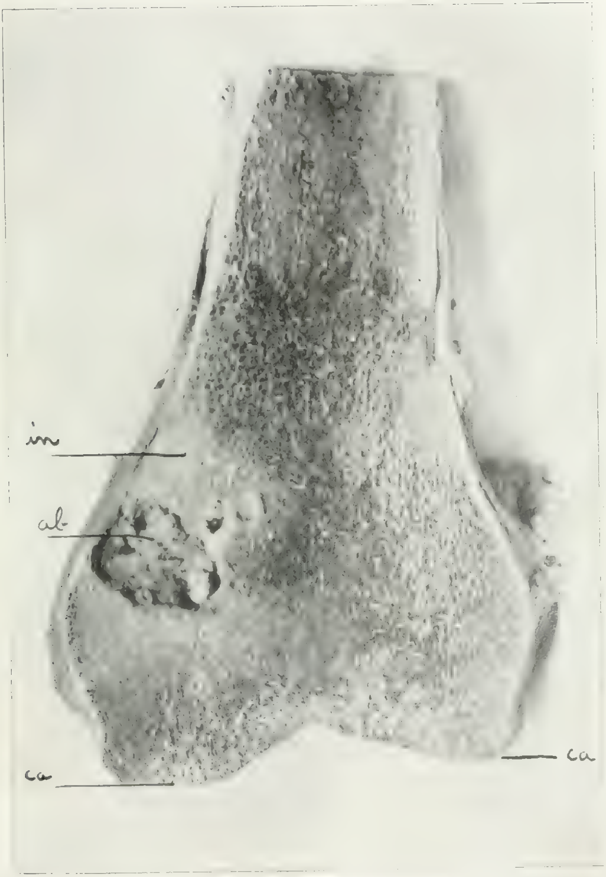


Fig. 4.—Longitudinal section of femur shown in Figure 3: *ab*, abscess in the epiphysis; *in*, infected area, the shape of which suggests infarction; *ca*, eroded articular cartilages.

in removal) were a number of small nodes from 1 to 1.5 cm. in diameter, exuding a purulent fluid on pressure. The right lung weighed 800 gm. The upper lobe was small, firm and covered with a thick fibrous pleura almost cartilaginous in consistence. It contained many solid yellow regions enclosed by radiating bands of fibrous tissue, from which a light yellow purulent material was easily expressed. In the main bronchus of this lung a small opening was found leading into a fistulous passage which extended for a distance of 6 cm. and terminated in a small cavity in the upper lobe. The cavity was irregular, about an inch in diameter and communicated with a small bronchus. Examination of the middle and lower lobes revealed conditions similar to those in the opposite lung (Fig. 1).

The pericardium was normal. In the heart were found a patent foramen ovale and fenestrations of the Thebesian and aortic valves; the other valves were normal. The myocardium was pale, but no nodules were found in a careful examination.

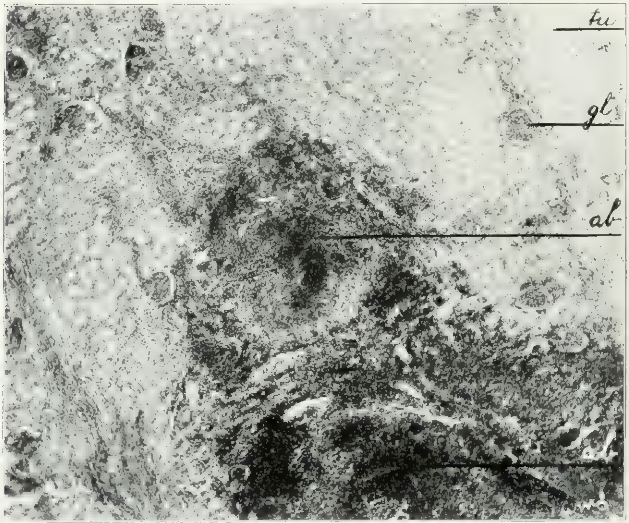


Fig. 5.—Photomicrograph of a blastomycotic abscess of the kidney: *tu*, kidney tubules; *gl*, glomerulus; *ab*, small abscesses which have become confluent.

The pharynx, tonsils, larynx, trachea, and thyroid gland presented no important changes. The anterior portion of the tongue on the left side was somewhat swollen and its surface was roughly granular. The peribronchial and aortic lymph-nodes were enlarged and pigmented and contained a number of yellow nodules.

The peritoneum was smooth and shiny. The mesenteric lymph-nodes were enlarged but contained no nodules. The liver (1,380 gm.) was smooth and dark red. The cut surface was mottled, and after hardening, three very small nodules were found in the interior after considerable search. The spleen weighed 170 gm., was quite firm and had a thickened capsule and trabeculae. Eight small blastomycotic nodules were found in its substance. There was a slight atrophy of the adrenals and pancreas and in the latter a small blastomycotic nodule was found. The gall-bladder and bile-ducts were normal. The stomach was small, its walls were thickened and the mucous membrane dark gray and covered with tenacious mucus. No changes were noted in the intestines, except pigmentation of Peyer's patches.

The kidneys were enlarged and, except for a depressed scar on the surface of the right kidney, the same description applies to both. On section, the cortex was increased in thickness, pale, and rolled out beneath the capsule. The latter stripped readily, leaving a smooth surface and beneath it, as well as on the cut surface, were a number of blastomycotic nodules from 2 to 9 mm. in diameter. A yellow purulent material could be expressed from the largest of these (Fig. 2). The nodules were less numerous in the left kidney. The bladder, prostate gland and testicles appeared normal.

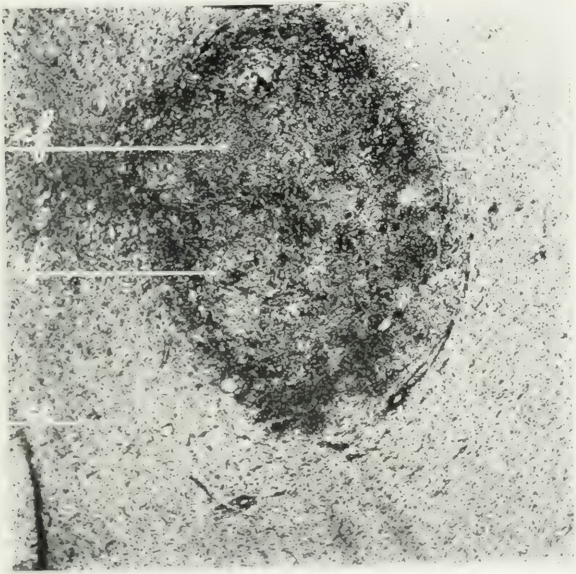


Fig. 6.—A photomicrograph of a blastomycotic abscess in the cerebrum: *cc*, cerebral cortex; *cf*, confluent foci of infection.

The brain externally presented no changes. After hardening, three small blastomycotic nodules were found in the cerebrum and one in the cerebellum.

The abscesses beneath the scalp were associated with two deep erosions, one in the occipital bone extending to the dura mater, the other in the parietal bone extending to the internal table. The abscess over the sternum communicated with an opening in the manubrium. On section, the greater part of the marrow of the bone appeared to be involved in a suppurative osteomyelitis. On the right side necrosis and softening had taken place and an irregular abscess cavity was present. The adjacent marrow compartments were filled with yellow pus to the extent that only a small portion of the left half possessed the normal red color. Local abscess formation existed in the first, fifth, sixth and ninth ribs on the right side and in the seventh and eighth ribs on the left side. In nearly all cases the abscess involved the entire shaft, producing a swelling an inch or more in diameter, and in some a diffuse yellow purulent infiltration was found extending some distance from the abscesses. Another large abscess in the pelvis was associated with an area of bone destruction 10 cm. in diameter involving the sacrum and adjacent portion of the right ilium and extending nearly through the bone. The right knee presented a diffuse purulent infiltration of the synovial and periarticular tissues, and some erosion of the head of the tibia was found. Similar conditions were present about the left knee, which contained a still larger amount of pus. The articular cartilages were in some places completely eroded and the surface of the bone hard and smooth (Fig. 3). Two communicating openings into the end of the femur were found, one on the inner side above the internal condyle, and another posteriorly between the condyles. In longitudinal section an abscess 2 cm. in diameter was found beneath the periosteum, just above the internal condyle. The surrounding cancellous bone was softened for a distance of several millimeters. Beyond this the bone presented a yellowish appearance in marked contrast to the red color of the unaffected bone. The softened area with the abscess was distinctly wedge-shape and suggested infarction (Fig. 4).

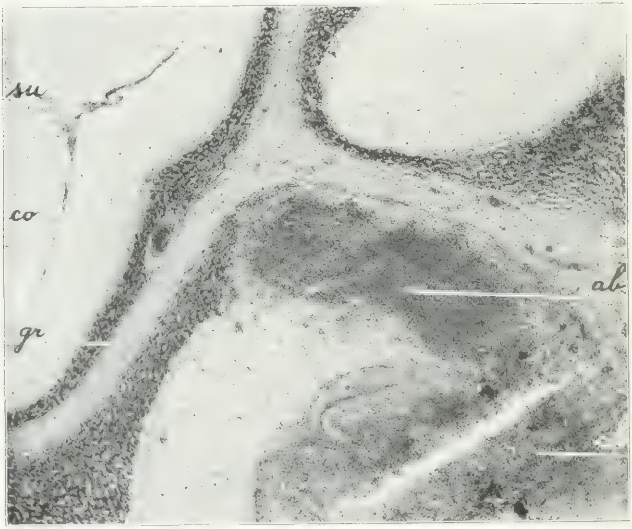


Fig. 7.—Photomicrograph of a blastomycotic abscess of the cerebellum: *ab*, abscess; *gc*, giant-cells; *su*, sulci between the convolutions; *co*, cortex; *gr*, granular layer.

Another lesion involving the periosteum and underlying bone was found in the right tibia at about the middle of the shaft. The abscesses about the small bones of both feet and the right wrist were opened and such marked destruction found that the anatomical structures were recognized with difficulty. Blastomycetes were easily demonstrable in the pus of all the bone lesions.

Histological examination of the nodules found in the various viscera demonstrated the blastomycotic nature of all of them. They possessed so many features in common that it is not essential to describe them in detail (Fig. 5). A rather marked peculiarity was found in the sections of the single nodule of the pancreas, for without the connective-tissue wall surrounding a region of necrosis and numerous organisms, there was no enveloping zone of round cells as is usually found.

The nodules in the cerebrum appeared as though they were caused by the localization of a considerable number of organisms at adjacent points (Fig. 6). The location of the nodules in the cerebellum were chiefly in the granular layer, and an apparent connective-tissue wall was present in and about some of them (Fig. 7).

In the lesions of the bone well-marked walls of granulation tissue were not present about the necrotic areas, and in the adjacent marrow compartments organisms were found unassociated with any tissue reaction.

Bacteriology.—Cultures were made at the necropsy from the blood, pleural fluid and the pus from various abscesses which had not been opened during life. No growth was obtained from the blood or the pleural fluid, but from the pus pure cultures of blastomycetes were obtained. They differed in no respects from those obtained during life from the pus of other abscesses, and a report of their cultural characteristics will be included in a subsequent comparative study.

Thanks are due Dr. E. C. Ryerson, attending surgeon, for permission to report this case.

A CASE OF BLASTOMYCOSIS

T. H. BOUGHTON, M.D., AND S. N. CLARK, M.D.
LAWRENCE, KAN. HOSPITAL, ILL.

Case XXIII (5).—*History.*—J. C., man, aged 21, entered Cook County Hospital, Aug. 21, 1907, to the orthopedic service of Dr. E. W. Ryerson. He was born in Italy, moved to the United States at the age of 1 year, and lived in Chicago since. He went to work at the age of 14, and has been engaged in peddling and factory work. For several months previous to his illness he worked in a tobacco factory and inhaled considerable tobacco dust. He also chewed considerable tobacco while in the factory. When at home he lived under fair hygienic conditions, but during the fall preceding the onset of the disease, after getting into trouble and being expelled from home, he slept in exposed outbuildings and basements. The previous and family history are unimportant.

He caught cold Nov. 15, 1906, and was confined to the house for two weeks, coughing frequently and expectorating bloody sputum at this time. He went to work December 1, and noticed pain in back of neck, and in right side of chest, and was obliged to stop work in a few days because of weakness, especially in the left arm, and was then confined to bed until December 27. At this time he suffered with pain in the back, bloody expectoration and night sweats. After January 1 he improved sufficiently to go to work, but, owing to weakness, was again obliged to return to his home, where he remained for the next five months. He coughed, expectorated bloody sputum, suffered pain in back and was quite weak. On May 30 he fell and hurt his back. From that time urination and defecation were involuntary. Two days after the fall he came to the hospital, complaining of pain in side, which was strapped, and he returned home, but the pain persisted for two weeks. On July 1 he was sent to Dunning, where he remained for one month in the tuberculosis hospital; two weeks of this time he was in bed. On August 21, as previously stated, he entered the hospital complaining of painful cough, weakness of the legs and involuntary evacuations. A kyphosis at the level of the second dorsal vertebra was noticed at this time, and in the examining-room the disease was considered tuberculosis of the lungs and spine.

Three weeks after entering the hospital (September 15), he fell while walking about the ward, and was thereafter unable to walk, owing to partial paralysis, and about one month later the paralysis of the legs became complete. Sensation was much diminished in the legs, but was never completely lost. The knee-jerks were increased; ankle-clonus and Babinski's sign also were present. Up to this time the diagnosis of tuberculosis had not been questioned, but the failure to find the tubercle bacilli in the sputum, together with the presence of numerous cutaneous lesions, gave rise to suspicions of blastomycosis. Examination of the unstained sputum and pus from various abscesses was undertaken with the result, at this time quite surprising to us, that the organisms were found quite abundantly present in both.

Examination.—An examination about December 1 revealed the following conditions: The patient lies quietly, seems comfortable, is unable to move the lower, and experiences some pain on motion of the upper extremities. Emaciation is marked and the skin is harsh and dry. He coughs occasionally and expectorates a purulent blood-tinged sputum. The voice is husky and evacuations are involuntary. On the left cheek near the nose is a dull red, slightly indurated, sharply outlined, flat crusted area, 2.5 cm. in diameter, marking the rupture of an abscess, part of which remains as a slightly red fluctuating mass, about 3 cm. in length, extending downward and outward. On the right cheek, in front of the ear, is a reddish pigmented scar, 2 by 3 cm. at the upper portion of which is a sinus communicating with an abscess the size of a hickory-nut. There is an abscess several times larger at the base of the neck on the left side. The cervical lymph-nodes are enlarged. Several small firm, painless irregularities are present on the ribs, and a tender point on the right fourth rib, in the axillary region. The lungs are hyperresonant with the exception of the right apex anteriorly and the upper lobes and upper portions of the lower lobes posteriorly, over which resonance is impaired and dry râles, bronchial breathing and bronchophony are heard. Over the remainder of the lung the respiratory sounds are roughened and prolonged. The area of heart dulness is normal, the tones clear and regular.

The abdomen is distended and tympanitic and contains no masses or tender regions. The liver extends to two fingers below the costal margin. The spleen is easily palpable, and on deep inspiration extends three fingers' breadth below the costal arch. At the point of the kyphosis previously mentioned a large flat abscess is present which is 10 cm. in diameter, and on the posterior surface of the right shoulder is another, soft and fluctuating and 7 cm. in diameter. A third is present on the left arm and from it small quantities of bloody pus escape. Decubital ulcers are present on both heels and over the sacrum.

An examination of the nervous system demonstrated no changes in reflexes of eyes and upper extremities. The abdominal and cremasteric reflexes are present, although less marked, on the left side. The lower extremities are paralyzed and foot-drop is marked. The patellar reflexes are very weak and the Kernig and Babinski reactions, the Achilles reflex and the ankle-clonus are all now absent. The plantar reflexes are exaggerated and stimulation of the plantar surfaces causes flexion of the thigh and leg, although voluntary motion is absent. Sensation to heat and cold are entirely lost, and to touch and pain much diminished.

Leukocytes and granular casts were often found in the urine, which was usually of low specific gravity. Albumin was absent until the last part of his illness and no blastomycetes were found in the sediment.

An examination of blood, Dec. 5, 1907, showed red cells 4,972,000; hemoglobin 75 per cent. (Talqvist); leukocytes 20,800. In a differential count there were neutrophils 84.3 per cent.; eosinophils 0; basophils 0; small lymphocytes 7.3 per cent.; large lymphocytes 8.3 per cent. Enormous numbers of blastomycetes were regularly found in the sputum, but no tubercle bacilli were demonstrated in repeated examinations. Bouillon inoculated with blood removed from the midvein of the arm, Dec. 3, 1907, remained sterile. Subcutaneous inoculation with tuberculin, Nov. 14, 1907, produced no reaction, but a conjunctival reaction was obtained ten weeks later.

The patient remained in the hospital until his death, which occurred March 14, 1908, a residence of seven months. The course was progressively downward, though some of the symptoms were much abated, and there were periods when the general condition seemed much improved. During November the cough, which at first was very troublesome and painful, ceased to be annoying. The sputum, which in the beginning was profuse and blood-tinged, became much less in amount and the blood disappeared. During January a small amount of voluntary motion returned to the legs. The abscess over the lumbar spine disappeared entirely, but the abscess at the base of the neck became larger and the kyphosis more pronounced, and some crepitus could be obtained over this region. About January 1, pain and tenderness appeared in the left knee and soon afterward both knees and ankles were involved in a suppurative process, which formed discharging sinuses. These joint manifestations were extremely painful, especially during the last month of life.

The temperature was about normal most of the time; often it was subnormal, and occasionally it rose as high as 101 F. for a few hours or a day. The pulse was rather rapid but extremely variable, ranging from 70 to 130 per minute. The respirations ranged from 22 to 28. During the last two months of life the pulse was constantly above 100, the temperature usually normal or subnormal (occasionally as high as 100) and the respirations averaged about 26.

The patient was given tonics until December 1, calcium iodid, 2 grains, every half hour until January 18, and then potassium iodid from 10 to 30 grains, four times a day.

Necropsy.—(Dr. Stober.)—Permission for a limited necropsy was secured March 15, one day after death, and performed under circumstances which are responsible for the incompleteness of certain portions of the examination. The body had been embalmed and cultural work was not possible.

Anatomical Diagnosis: Multiple blastomycotic lesions of the skin, subcutaneous tissues, muscles and bones; blastomycosis of the lungs, peribronchial lymph-nodes, and spleen, passive congestion and edema of the lungs, parenchymatous degeneration of the kidneys and liver; bilateral fibrous pleuritis; decubital ulcers; anasarca; kyphosis; general emaciation.

The upper part of the body showed extreme emaciation in contrast to the abdomen and lower extremities, which were markedly edematous. Decubital ulcers the size of the palm were present over both hips. On the left side of the face was a circular scar with margins still red and slightly crusted. A small fluctuating area could be felt in the deep tissues beneath. Another marking the site of an old abscess was present in front of the right ear. Behind the right shoulder was found a large fluctuating abscess which seemed to be confined to the subcutaneous tissues; a much larger one was found over the upper part of the spine extending to either side for a distance of several inches. A kyphosis of the spine involving the last cervical and the first two dorsal vertebrae was present at this point. The spines of the vertebrae were separated from each other more than usual, and manipulation of the spine of the first dorsal, which was the most prominent, elicited a distinct crepitus The kyphosis could be reduced and exaggerated to a considerable extent by extension and flexion of the neck on the chest. An external incision was here not allowed.

An examination of the fistulas connecting with underlying abscesses over both knees and ankle-joints demonstrated eroded bone at their bases, but further examination of the bones was not allowed. On opening the chest, the pleural cavities were found practically obliterated by fibrous adhesions. These were very firm at the apices, especially on the right side, where dense cicatrical masses were present. The lung was torn at this point on removal and presented a fistulous opening which communicated with a cavity in the upper lobe, and extended posteriorly between the first and second ribs, the adjacent margins of which were sharp and eroded. No direct communication with the abscess in the back could be demonstrated by pressure on the latter.

The bodies of the vertebrae from the front appeared normal. The anterior surface of the second thoracic was covered with the fibrous tissue involving the right pleura. This vertebra was removed with the bone forceps, and a small portion of the spinal cord was exposed but appeared normal. The cancellous tissue of the bone was normal. Further examination of the vertebrae and back was not allowed.

The lungs together weighed 1,100 gm. Both showed thickened pleurae with numerous fibrous tags. The upper lobe of the right lung was torn in removal as described. This lobe was small and quite solid, although slight crepitation could be obtained in the lower portion. In the upper portion of the lower lobe and in the middle lobe could be felt a number of nodules. On section, the greater part of the posterior portion of the upper lobe was occupied by an irregular cavity which communicated with one of the bronchi. The main bronchus was dilated to form another small cavity at about an inch from the bifurcation. The surrounding tissue was fibrous in character and contained a number of yellow necrotic regions measuring from 3 to 6 mm. in diameter. Between these and also in the anterior portion of this lobe, the middle lobe and the upper half of the lower lobe, were numerous miliary nodules, some of the larger of which were necrotic. Coal pigment was present to a considerable extent, especially in the affected parts of the lung. Considerable frothy fluid could be expressed from the lower lobes (Fig. 1). The left lung crepitated freely throughout, except at the apex where a large radiating scar was present, extending into the lung for a distance of several centimeters. On section, the lung was dark red, and bloody frothy fluid could be expressed. Small nodular fibroid masses throughout the lung were cut through. The bronchi were here as well as in the opposite lung thickened and prominent. The peribronchial lymph-nodes were enlarged, from 1 to 3 cm. in diameter, and dark red to black on section. Two of them contained several small encapsulated necrotic regions and also a few miliary nodules.

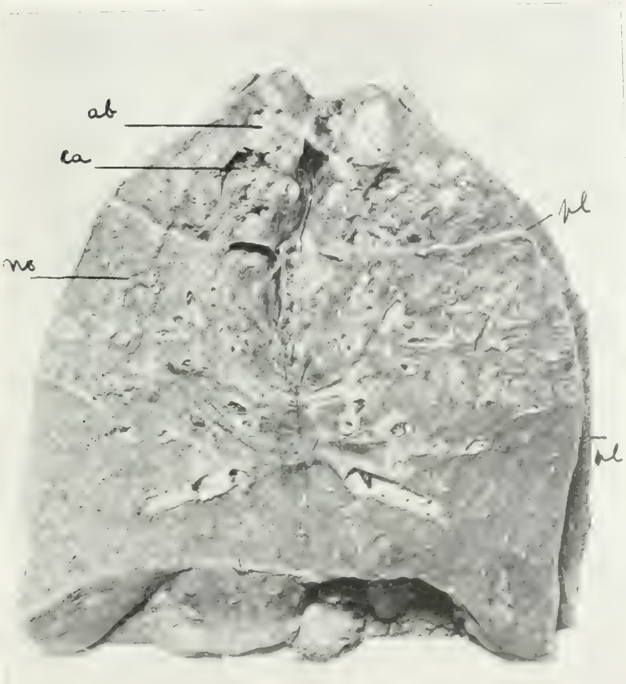


Fig. 1.—Right lung, Case 23: *ca*, bronchiectatic cavity in the fibroid upper lobe; *ab*, abscesses whose contents were inspissated and surrounded by a wall of connective tissue; *no*, blastomycotic nodules in the lower lobe, which from their distribution seem to be bronchogenic in origin; *pl*, thickened pleura.

The heart, empty, weighed 255 gm. The pericardium on the anterior surface presented an area of fibroid thickening 3 cm. in diameter. The valves appeared normal. The musculature was a light brown, and in numerous sections no nodules were found. Nothing of importance was found in the thyroid, esophagus, stomach, intestines, pancreas, bladder, prostate or adrenals. The liver was much enlarged and its anterior margin was considerably rounded. The cut surface was light yellow and fat droplets could be seen in the material scraped from the surface. On section of a portion of the right lobe, one small nodule 2 mm. in diameter was found. The spleen was moderately enlarged. The surface was smooth and the capsule somewhat thickened. On section an excess of connective tissue was present, the Malpighian bodies were indistinct and a few miliary nodules were found.

The kidneys together weighed 260 gm. and were normal externally. The cortex was increased, measuring 7 mm. in thickness, and was pale yellow in contrast to the pyramids, which were light red and measured 20 mm. in length. The capsule stripped readily, leaving a smooth surface. No focal lesions were found in either organ.

Histological Examination.—Some difficulty was experienced in demonstrating the organisms in the necrotic material described in the right lung as being surronded by more or less marked masses of fibrous tissue. The lesions in other organs were similar to those described in other cases. Their blastomycotic nature was proved with the exception perhaps of the sections examined of the small nodule in the liver, in which no organisms were found. In other respects this too corresponded to blastomycosis. The sections of the other organs possessed changes indicated in the anatomical diagnosis. No lesions peculiar to blastomycosis were found in sections of the body of the second dorsal vertebra.

Bacteriology.—Blastomycetes were repeatedly demonstrated in the sputum and in the pus from the cutaneous lesions and the various abscesses during life, and pure cultures were obtained from the pus when the abscesses were aspirated or drained. In the mucus removed from the trachea and bronchi at the time of the post-mortem examination the organisms were found.

A CASE OF SYSTEMIC BLASTOMYCOSIS WITH RECOVERY

T. H. BOUGHTON, M.D., AND A. M. STOBER, M.D.
LAWRENCE, KAN. CHICAGO

Case XXIV (6).—*History.*—S. K., a native of Montenegro, aged 39, was admitted to the service of Dr. Slaymaker, April 12, 1908. It was learned through an interpreter that he had been in this country one year, working first as a laborer on a railway for five months, then for two months in Missouri laying pipes. During this time he spent half of each day in a ditch partly filled with water, but declares that he felt perfectly well. The next five months he lived in South Chicago and the last three months he was ill, owing to exposure while looking for work. He lived about two blocks from the lake on the second floor of a frame house built on low ground which was wet and muddy at that time of the year, November, 1907, to March, 1908. Seventeen persons slept in the five rooms on this floor; two or three of them were sick in bed with fever, and although he was unable to give many details of their illness he stated that there was a great deal of coughing. A small cooking-stove in a hall was the only source of heat for the entire second floor of this building.

No history of venereal infection was obtained and the family history was unimportant. This illness began in January, 1908, with intense pain in the chest, cough, fever and weakness. Blood was present in the sputum at first and has continued to appear at intervals since. During the two weeks before his admission to the hospital a number of abscesses developed and the dorsal surfaces of both feet became swollen and tender. He has lost some weight but does not know how much. When he entered the hospital he complained of pain in the feet and ankles. An examination at this time revealed a slightly reddened superficial ulcer about the size of a finger-nail over the left supra-orbital ridge. It was covered with a thick crust under which was bloody pus. Similar lesions were present on the lower right eyelid near the nose and over the angle of the right scapula, and also small pustules on each arm just above the left external malleolus. There were three smooth pigmented scars on the right thigh which the patient ascribed to some running sores connected with the bone, which he had when a boy.

He was well developed and well nourished and obviously not very sick. There was no evidence of consolidation found in the examination of the lung. Slightly impaired resonance was obtained over the right apex and a few crepitant and subcrepitant râles were heard over the region and over both lower lobes. The area of cardiac dulness was increased to the left 2 cm. The inguinal lymph-nodes were moderately enlarged.

About May 1 no râles could be heard in the lungs. Otherwise the pulmonary examination disclosed nothing new. A crusted lesion had appeared on the back of each hand. The pustule on the left leg had developed into an ulcerated crusted lesion 3 cm. in diameter and discharged considerable bloody pus. A subcutaneous abscess 5 cm. in diameter which had developed about the right external malleolus was opened and a large amount of dark bloody necrotic material escaped, and in this blastomycetes were found and pure cultures obtained.

The upper end of the right tibia was very tender, and the overlying skin was red and edematous. The dorsal surfaces of the feet were swollen and tender, walking was decidedly painful and the patient's general condition was somewhat worse. A month later the patient was confined to bed by weakness. The tenderness and redness over the right tibia had disappeared and a small subcutaneous

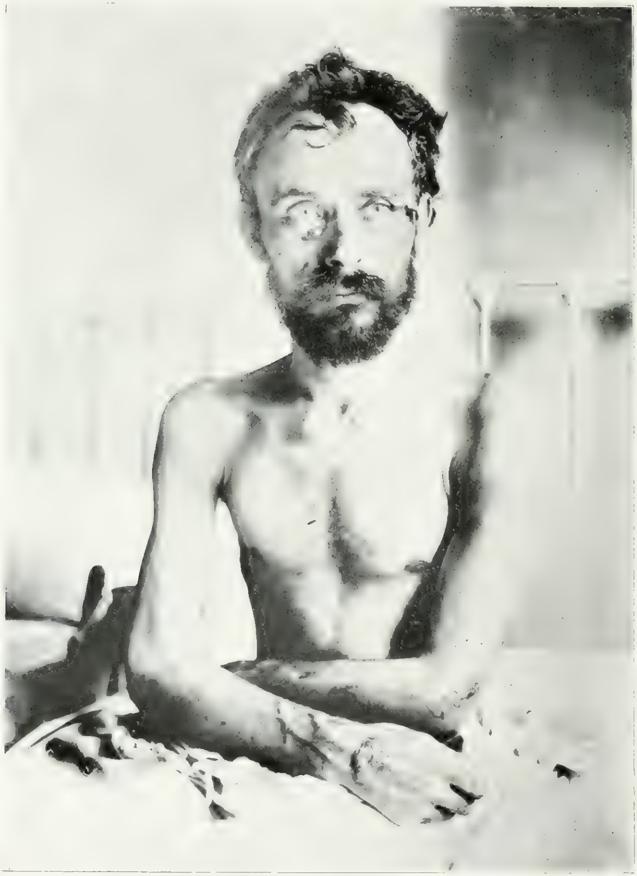


Fig. 1.—Case 24. This photograph was taken shortly after the vaccine treatment was begun. Three lesions on the face, three on the left forearm and one on the right hand can be distinctly seen.

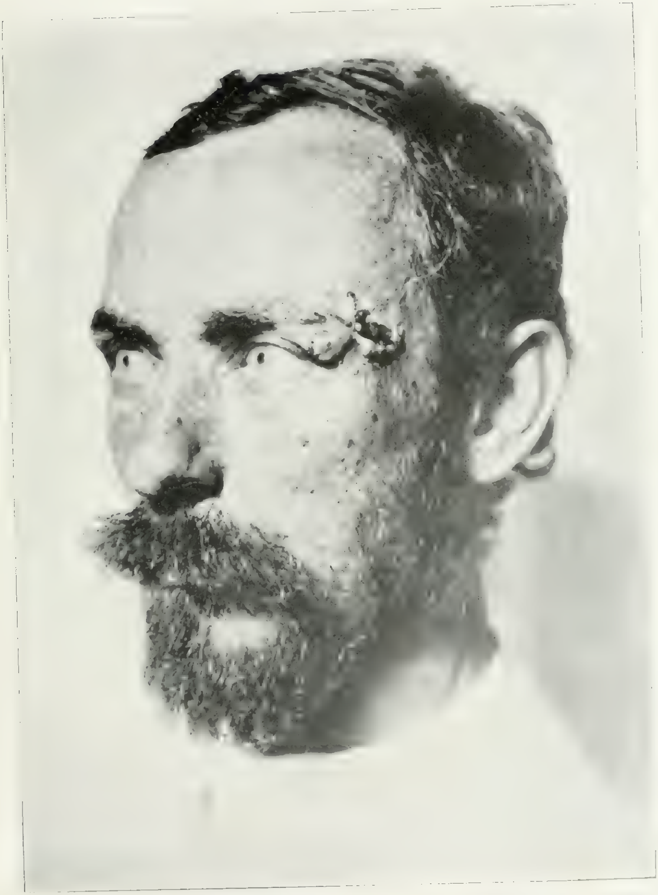


Fig. 2.—Case 24. Taken during the latter part of August, six weeks after beginning of vaccine treatment. The lesions on nose and under right eye have disappeared. The one present near left eye is much improved.

abscess had developed near the attachment of the patellar ligament. The tenderness and swelling on the dorsal surface of the right foot had disappeared completely, and a small subcutaneous abscess had developed on the dorsal surface of the left foot. A small area of redness, tenderness and swelling had appeared over the middle of the left tibia, and a small pustule had developed over the spine of the right scapula. The sputum was still occasionally tinged with blood.

During June two small lesions developed on the nose, one on the right cheek (Fig. 1), six lesions on the left arm (three on the extensor and two on the flexor surface of the forearm, and one on the back of the elbow), one on the back of the left thigh, one on the anterior surface of the right thigh, and one on the outer aspect of the left leg below the knee, making a total of twenty-four distinct superficial lesions, only six of which were present on admission.

It is interesting to note that the arrangement of the lesions was roughly symmetrical. Until July 10 improvement was noted in only two of the lesions in spite of the fact that patient had been under treatment with potassium iodid and copper sulphate from the time of the discovery that the disease was blastomycosis and not rheumatism, for which he had previously been treated. One of these lesions was a small cutaneous abscess at the angle of the scapula which had never been large or deep. This had ceased to discharge and at this time was red and indurated. The other lesion was a swollen tender area on the dorsal surface of the right foot which lasted about three weeks and did not suppurate.

The sputum on repeated examinations showed no tubercle bacilli, but constantly a few blastomycetes. The urine in a number of analyses showed nothing abnormal. An examination of the blood made early in the course, April 30, 1908, demonstrated 5,748,000 red cells and 90 per cent. hemoglobin (Talqvist). The white cells numbered 18,300, of which the polymorphonuclear cells constituted 75 per cent., small mononuclears 17 per cent., large mononuclears 6 per cent. and eosinophils 2 per cent.

Vaccine Treatment.—A vaccine treatment was instituted July 10, and consisted of the subcutaneous injection of the filtrate and suspension of the blastomycetic mycelium obtained from cultures grown in glucose bouillon at room temperature. The temperature up to June 1 ranged from 99 to 100.4 F. and from June 1 to July 10 from 99 to 99.8 F. Seven hours after the first injection (July 10) a maximum temperature of 100.8 F. was noted, returning to normal after two days and remaining so except after the subsequent injection of vaccines, when increases of from 0.4 to 1.4 F. were obtained. With the rise of temperature occurred also a distinct inflammatory reaction about the lesions consisting of pain, redness, swelling and increased discharge, and also a general feeling of malaise. After the second injection, July 15, an active healing of the lesions occurred. The vaccine used in the third injection, July 22, was prepared from cultures of a mold obtained from wood (Fig. 19, p. 537), and the reaction obtained was even more marked and prolonged than from the vaccine prepared from the cultures of blastomycetes. A deep abscess in the right arm suddenly enlarged, approached the surface and ruptured. The site of the injection also became red and indurated and from the swelling a few days later a small quantity of sterile pus was aspirated. The patient by this time was able to walk about in the yard.

Two more injections were given August 10 and August 24, with the result that on September 1 seventeen of the twenty-four lesions previously noted had disappeared. The lesions remaining were still red and indurated but the discharge had ceased and they were much smaller (Fig. 2). The healed or healing condition of the bone lesions was quite apparent in roentgenograms taken at this time and reference to these is made by Dr. Potter, roentgenographer, in a review of the subject (p. 541). On examination of the chest impaired resonance was obtained over the right lung posteriorly with harsh breath-sounds over this area and the upper portion of the left lower lobe. A few dry râles were heard over the right side. The patient's general condition was much improved and

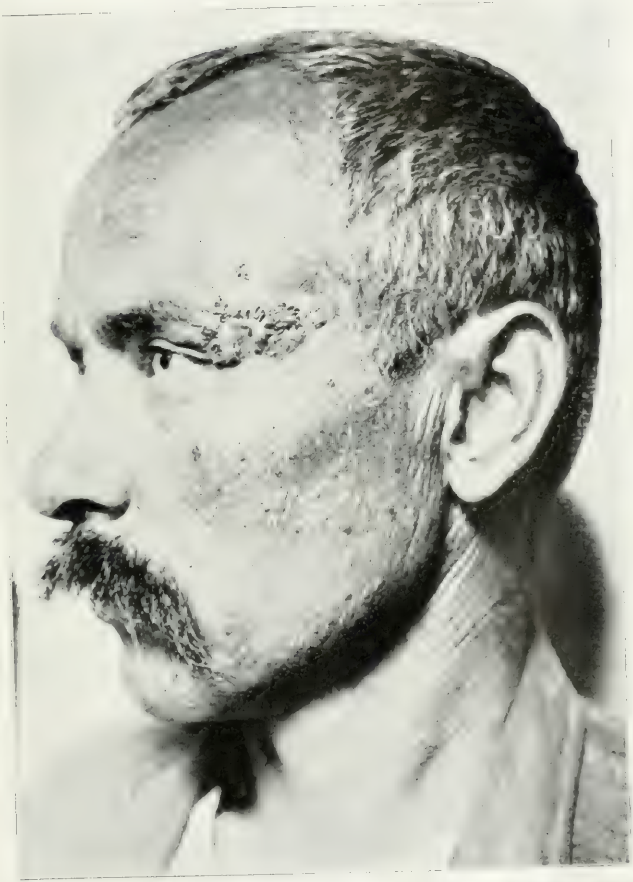


Fig. 3.—Case 24. Taken during latter part of September, showing nearly healed condition of lesion near the left eye.

he gained considerably in weight. Other injections were given September 17, October 13, October 31, November 15 and December 1, when they were discontinued. Of the twenty-seven lesions, all but two seemed to be healed: one on the right forearm, and one on the left side of the forehead (Fig. 3). The patient had gained much in weight and felt better.

The results of the blood examination made September 17 were as follows: white cells 11,000; polymorphonuclears 65.6 per cent.; small mononuclears 21.8 per cent.; large mononuclears 10 per cent.; transitional cells 1.8 per cent.; eosinophils 0.6 per cent., and myelocytes 0.0 per cent. On September 19, 15,300 whites were found, an increase of 4,300 two days after injection of vaccines. Other counts October 13 and October 31 showed little variation from the above except for the increase of large mononuclears to 17 per cent. and the presence in some of these of fine neutrophilic granules, thus approaching the myelocyte in type.

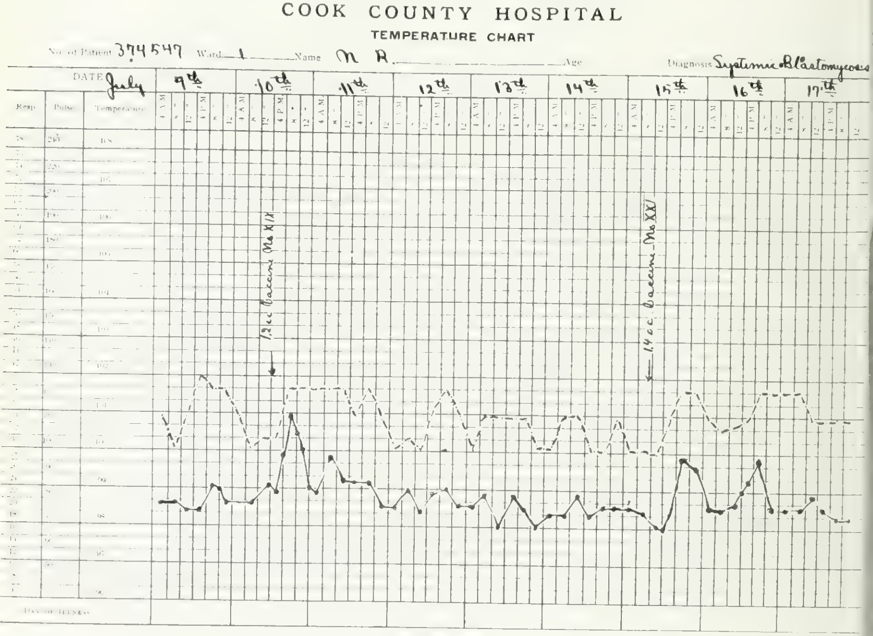


Figure 4.

On December 9 the patient furnished the blood for a venous transfusion and was quite weak for a few days but seemed to regain his strength. During January he began to lose weight and the lesion on the right forearm began to discharge. On February 1 a small papillomatous growth appeared on the right ala of the nose and an abscess on the dorsum of the right foot. The latter was opened and drained and the administration of potassium iodid and vaccine (2 c.c. every tenth day) was again resumed, with the result that by April 1 the lesions on the arm and nose were practically healed, but the abscess on the foot was still discharging slightly. On April 21 he began to complain of a pain in the left chest which increased in severity and was associated with the appearance of physical signs of fluid in the left chest. On May 4 the left chest gave a flat note on percussion below the level of the middle of the scapula; voice-sounds were diminished and breath-sounds absent. At this time the patient was confined to bed and given potassium iodid in doses increased for 20 to 85 grains three times a day and vaccine filtrate from 1 to 3 c.c. every tenth to fourteenth day. A gradual improvement occurred and on June 1 the patient was allowed to walk about in the yard. All evidences of fluid in the chest had disappeared. He left the hospital June 19, at which time slight dulness with increased transmission of breath- and voice-sounds were still present over the apices, especially the left, but the cutaneous lesions and the abscess of the foot were apparently healed.

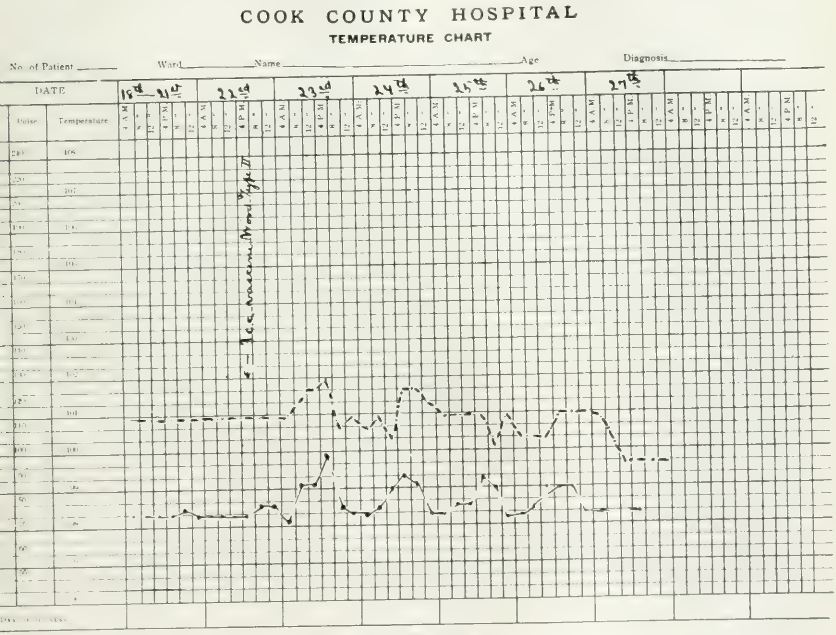


Figure 4.—Continued.

These results indicate that in this case at least the subcutaneous injections of old cultures of blastomycetes were of undoubted benefit. A local reaction in the lesions and a rise of temperature followed each injection (Fig. 1, temperature chart). The intensity of the reaction was also proportionate to the quantity used, taking into consideration, of course, the immunity which was being acquired. It will also be noted that the culture of the mold from the wood was even more active than the culture obtained from the pus, and that the blastomycetic filtrate was more efficient than the suspension of the triturated growths. Inoculation tests made by applying sterilized bouillon filtrate and mixed cultures triturated in lanolin to the skin which had previously been scarified, gave negative results.

Further inoculation tests were made by Dr. Boughton, with three suspensions of blastomycetes very kindly furnished by Dr. L. Hektoen. Two of these organisms were from Christensen and Hektoen's two cases, and the other organisms isolated by Dr. H. T. Ricketts. A drop of each of the suspensions was placed on the skin of the forearm and the underlying skin scarified. No reaction was observed. Ten days later the test was repeated on the opposite arm using a minute puncture after the manner of Pirquet. In twenty-four hours a distinct papule was present at the site of each inoculation and persisted for four days. The control puncture showed nothing. The ophthalmic test was negative. Inoculation tests by both methods mentioned in several normal cases, and ophthalmic tests in three normal cases gave uniformly negative results.

Thanks are extended to Dr. Slaymaker for permission to report the case.

A CASE OF SYSTEMIC BLASTOMYCOSIS

H. JACKSON, M.D.
CHICAGO

CASE XXV (7).—*History.*—M. M., a native of Croatia, entered the Cook County Hospital May 27, 1908, to the service of Dr. Elliot. He spoke no English and a history was obtained with difficulty. His illness began one year ago with a cough and profuse expectoration which became gradually worse and was associated with considerable loss in weight. Three weeks before entering the hospital a swelling with pain and tenderness appeared in the left arm followed by a swelling of the forearm and hand. A week later ulcers developed in the skin of the face and other parts of the body and progressed quite rapidly.

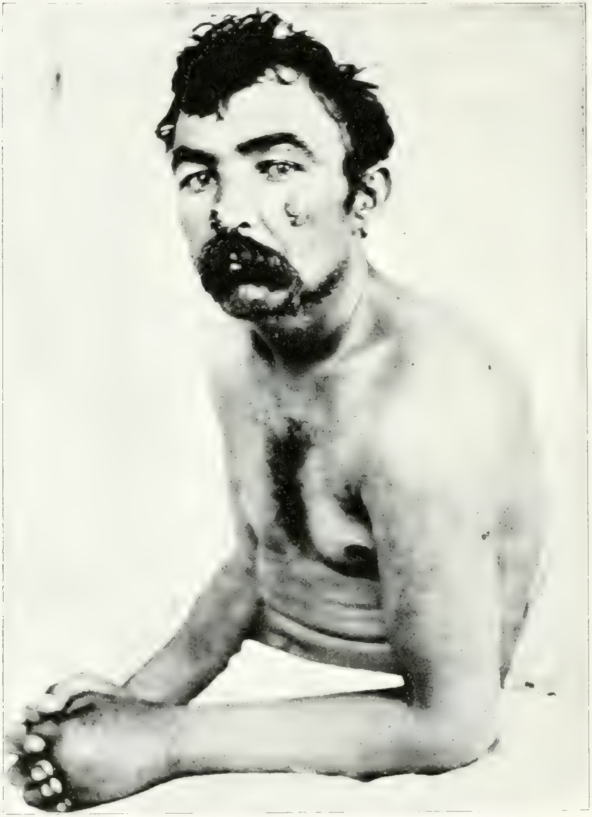
The family history was unimportant. The patient had experienced no serious illness and no venereal infection. He had been a farmer but after coming to this country a year ago he worked as a laborer on a railway. For the previous three months he was unemployed and lived in South Chicago. He drank considerable beer and whisky and smoked many cigarettes each day.

On examination the patient stated that he felt well and desired to return to his native land. He appeared somewhat emaciated and coughed frequently, expectorating bloody purulent sputum. The respirations ranged from twenty-four to thirty, the pulse from 90 to 100 per minute, and the temperature from 98.6 to 101 F. At this time there was on the nose an oval papillomatous lesion from 2.5 to 3.5 cm. in diameter with a raised margin and a base covered with a blood-stained crust under which was a quantity of brown pus. A similar lesion 2 by 3 cm. in diameter was present on the left cheek. Other smaller lesions were present on the left arm within the area of induration previously described, over the left scapula, the coccyx and on the scrotum. A larger one 3 by 4 cm. in diameter was found on the left buttock.

No changes were found in the scalp, eyes, ears or throat. Anteriorly in the neck small, hard lymph-nodes were palpable. The indurated upper half of the left arm was extremely tender, and fluctuation was obtained in its inner border. The forearm and dorsum of the hand were edematous and the arm could not be moved without considerable pain. (See accompanying illustration.) The joints and other extremities were not affected. The respirations were frequent, the supraclavicular and infraclavicular spaces deepened and the apex-beat of the heart not visible. Percussion elicited impaired resonance over the upper lobes on both sides, where tactile fremitus was increased. Over the right side of the chest posteriorly bronchial breathing and prolonged and high-pitched expiratory sounds were heard. On the left side over the upper lobe there were harsh breath-sounds but no râles.

The area of cardiac dulness was not increased, and the sounds were normal. The arteries were sclerotic, the pulse full, strong and regular. The abdomen was distended and tympanitic; the liver and spleen not palpable. At the middle of the external surface of the left testicle was a hard nodule 1 cm. in diameter. The epididymis also contained a hard nodule the size of a split pea. The right testicle and prostate were normal. No changes were found in the nervous system. Examination of the blood revealed 65 per cent. hemoglobin (von Fleischl) and 13,000 leukocytes; the polymorphonuclears numbered 90.4 per cent., small lymphocytes 4.8 per cent., large lymphocytes 2 per cent., eosinophils 2 per cent. and basophils 0.7 per cent.

Bouillon inoculated with blood from the median vein remained sterile. The urine was clear, amber in color; specific gravity 1.015; reaction acid; no albumin or casts present.



Case 25.—Cutaneous lesions on the nose, left cheek and shoulder, also a swollen condition of the left hand secondary to an abscess in the arm.

Many blastomycetes were demonstrable in the sputum, but tubercle bacilli were absent. Round and budding blastomycetes were found in the pus from the cutaneous lesions and the abscesses, and afterward cultures were obtained.[1]

On account of his desire to return to Croatia, he left the hospital unimproved four days after admission.

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[1] Reference to these is made in another place.

A CASE OF SYSTEMIC BLASTOMYCOSIS WITH NECROPSY

R. E. BECHTEL, M.D., AND E. R. LeCOUNT, M.D.
CHICAGO

CASE XXVI (8).—*History.*—On June 28, 1908, a Swede, J. F., aged 38, was admitted to the medical service of Dr. Mix, giving a history of illness beginning in the previous February with a cough, pain in the side and an expectoration occasionally blood-tinged. He had always been a strong robust man of good habits and when taken ill was working in a steam laundry from sixteen to eighteen hours a day. Shortly after the cold began he suffered from pain in the left hip and for this went to a hospital where the thigh was incised and a large amount of pus evacuated. A few days after this operation a papule appeared on the upper lip, suppurated and then became covered over with a crust. Similar lesions developed on the neck, chin, forehead, chest, abdomen and extremities in the order given, and also on the middle finger of the right hand, following, according to his statement, an abrasion. During this period in the hospital, which lasted five weeks, he lost greatly in both weight and strength and the cough and expectoration continued; his illness was considered as tuberculosis.

When admitted to the Cook County Hospital as stated June 28, he was unable to walk, greatly emaciated and dyspneic after much conversing or other slight efforts. The wounds in the thigh, two deep incisions, in which drainage-tubes were still present, were discharging freely and necessitated his lying quietly. The temperature was 101.2 F., respirations 36, pulse 144. Papillomatous ulcers from 2 to 4 cm. in diameter were present on the left side of the forehead, the upper lip on the right side, the back and left side of the neck and the right middle finger. There were many more subcutaneous abscesses which had not ruptured, located as follows: two beneath the scalp, one at the vertex and one over the right ear; two on the back; three on the abdomen; one in the right axilla; three in the left arm and forearm; three in the left thigh; two in the right thigh and one on the back of each leg. These abscesses varied from 2 to 5 cm. in diameter and were for the most part soft and fluctuating. (See illustration.)

Movement of the left thigh was resisted and deep pressure over the crest of the ilium caused considerable pain. The cervical and axillary lymph-nodes were moderately enlarged. Dulness and other signs of consolidation were present over the upper part of both lungs.

Treatment and Course.—The disease was quite promptly recognized as blastomycosis and the organisms found and isolated in pure culture from unbroken subcutaneous abscesses. Roentgen examination of the left hip revealed instead of a joint trouble, a circular defect in the left ilium slightly larger than a silver dollar, and a few weeks later by a similar examination a portion of the crest of the bone was seen lying loose in the abscess cavity. During the two months from the time of admission to patient's death, August 27, the most noteworthy development in the course of the disease was the demonstration of staphylococci and *Streptococcus pyogenes* in some of the unruptured abscesses during a period of slightly more fever and profuse night sweats. An antistreptococcus serum was administered without any marked benefit.

There was some slight improvement during these two months; occasionally the patient was able to spend a portion of his time in a wheel-chair. Some of the abscesses healed after opening and cleansing with iodin. The dyspnea increased toward the end and the physical examination of the chest revealed gradually increasing consolidation until all parts of both lungs were involved.

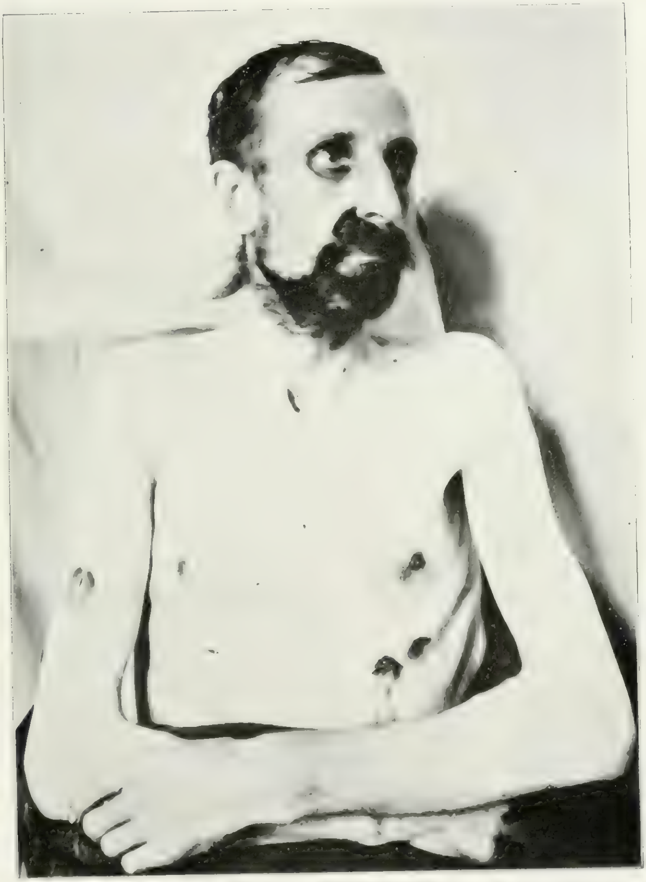
The leukocytes in the blood were never over 9,000 per cubic centimeter. Occasionally small sequestra were discharged from the wound in the left hip, which remained open; over the left ilium crepitus was obtained. In the sputum with the increased pulmonary consolidation the blastomycetes became very abundant; tubercle bacilli were never found. Shortly before death the appetite failed, albumin appeared in the urine and there was some edema of the lower extremities.

The patient was given ½ grain of copper sulphate three times a day and from 30 to 150 grains of potassium iodid. Three injections of a blastomycetic vaccine given in July were followed in each instance by a local reaction and some improvement; two more in August were without benefit.

Necropsy.—The post-mortem examination was held the following day after the body had been embalmed by arterial injection. The anatomic diagnosis was as follows: "ulcerative blastomycosis of the upper lobe of the left lung; disseminated blastomycosis of the lungs, liver, spleen, kidneys, adrenal, brain, subcutaneous tissues and skin; blastomycotic caries of the left iliac and right parietal bones; fibrinous and fibrous pleuritis; hyperplasia of the tracheobronchial, cervical and mesenteric lymph-glands; red marrow in the femur; emaciation; atrophy of the liver; fibrous mural endocarditis; ossification of the thyroid and costal cartilages."

The following are descriptions of the more important lesions: On the face, mostly on the right cheek but extending to the right ala of the nose, is an ulcer with elevated margins with a rather dry floor; 2.5 cm. in its longest diameter, which is downward and to the right into the yellow and rather long moustache. This is the only ulceration on the external surface of the body which has the appearance of any chronicity. The remainder are numerous, and are but little more than recently opened subcutaneous abscesses or the superficial and apparently acute destruction of the skin following such processes. The largest of these is over the left crest of the ilium about 15 cm. from the median line behind. Here is an opening 8 cm. in length with red inverted margins and packed with gauze and containing in its depths loose necrotic bone. The next largest lesion is located midway between the lower angle of the left scapula and vertebrae and consists of a purplish-red oblong necrosis of the skin 6 cm. in its longest diameter, in the middle of which there is an opening into which the terminal phalanx of the middle finger is easily passed into the abscess pocket between two ribs. There are smaller abscesses, the result of a rupture or opening of subcutaneous abscesses on the entire body. There are two on the right side of the face, one on the left side of the forehead, one over the thyroid cartilage, one in front of the left elbow, four on the anterior surface of the trunk, two on the anterior surface of the left thigh, one behind the right knee and one over the middle of the left calf; these are mostly small, from 1 to 2 cm.; gray or yellowish-brown pus can be expressed from them; their openings are small; the skin and subcutaneous tissues are determined. In addition to these are three brownish discolorations on the abdomen on the left side, slightly elevated and fluctuating. Two similar elevated, fluctuating swellings occur, one over the base of Scarpa's triangle on the right side, and another over the internal malleolus (right side). The last two are not discolored externally. These swellings are about the size of hazelnuts. That in the right groin is twice the size of the other; they all contain pus more or less blood-stained.

The changes in the lungs are quite alike. The two pleural sheets are adherent over a region at the apex of each lung equal to the entire palm of the hand in size. Both are fairly firm, probably from the embalming fluid in part, but also from the presence of innumerable closely set gray firm regions the size of miliary tubercles or slightly larger, which are scattered throughout both lungs; more discrete below, more confluent above. In the upper part of the left lung there are a few cavities the size of a hickory-nut. There are enlarged lymph-nodes about both sides of the trachea and in the cervical regions as high as the hyoid bone; there are more on the left side and larger. They vary from a buckshot



Case 26.—Photograph taken July 10, at which time the vaccine treament was instituted. Note the cutaneous lesion above the lip on the right side and the five abscesses in the chest and right forearm. Four had been recently incised, after painting with iodin.

to a hazelnut in size and are firm and red on the cut surface. Such lymph-nodes are also found about the roots of both lungs. The spleen has rounded margins; is 14 cm. long, has an unchanged surface, is firm, and on cutting there is an increased amount of pulp substance seen; it is not very bloody. The Malpighian bodies are distinct and there are a few grayish-yellow spots slightly larger than Malpighian bodies; they are not numerous.

The kidneys are slightly larger than normal and are unaltered except for scattered yellowish lesions mostly in the pyramids, from 1 to 4 mm. in diameter, and the larger ones with softened centers. Four or five such lesions are encountered in single vertical transverse sections. The ureters and bladder are unchanged. The prostate is enlarged. In each lateral lobe abscesses occur containing thick gray pus. On the surfaces exposed by vertical section into each lateral lobe there are a number of irregular cavities, the largest of which would contain a small pea. They are more numerous in the right lobe, in which a spongy or worm eaten appearance to the surfaces is given by the number of abscesses present.

Over the middle of the right parietal bone there is a necrosis of the pericranium 1.5 cm. in diameter. On the inside of the skull opposite this there is a slight yellowish exudate on the dura. The calvarium contains but little diploë. The skull here is thin; there is an extensive necrosis with sequestrum formation of the crest of the left ilium.

In the brain, which was examined very carefully,[1] fourteen small lesions were found in the cerebrum and a few in the basal ganglia and deeper parts of the hemispheres; but most of them were located at the bottom of sulci or at the junction of the gray and white substance. These nodules varied from 2 to 4 mm. in diameter. In the cerebellum there were two larger lesions, one 15 by 11 mm. in the white substance between the dentate nuclei, and above the nuclei, and a second slightly smaller 4 mm. posteriorly.

Histological Examination.—The changes found in sections afforded no essential additional information with the exception of the liver. In this organ minute focal lesions were very numerous. They were about the size of renal glomeruli, located as a rule well within the lobule, and possessed the features common to all the primary minute blastomycotic lesions. So far as could be ascertained the large oblong lesions in the distal portions of the renal pyramids originated from the location there of the fungi in the collecting tubules, and this explanation received some support from the occurrence of small local lesions in the cortex in which both glomeruli and tubules were involved. Characteristic changes occurred in the mediastinal, inguinal and periaortic lymph-nodes, but careful search failed to reveal any in the enlarged mesenteric lymph-nodes. In all the blastomycotic lymph-nodes the alterations varied from minute and widely scattered focal lesions to similar lesion so numerous and coalescent as to occupy practically all of the sections. The chronic changes in the upper lobes of the lungs resembled in the extensive necrotic regions a slowly progressing chronic caseous tuberculosis. In numerous sections there were encountered rounded regions of necrosis which represented occluded bronchi. In the lower lobes the changes were such as have been repeatedly described, the small regions of pneumonia, the replacing of one or more alveoli in some places with single minute blastomycotic focal lesions, in other places a number of such coalescent lesions. In some sections small regions of pneumonia due simply to the filling of the alveoli with leukocytes and fibrin were present; in many sections desquamated cells were abundant in the alveoli; in sections from the lower lobes some emphysema also was found. The regions involved in the adrenals were highly necrotic. In the prostate the sections contained simply abscess walls, and although the surrounding tissues varied, the abscess walls possessed a structure quite like that often met in the subcutaneous abscesses. Nor did sections of the brain lesions reveal anything new; on the whole there was but little tissue reaction, as has been the case with the brain lesions in other bodies previously examined. In some sections of the sternum made from the marrow taken at random and without reference to the presence or absence of contiguous abscesses, numerous lesions in all respects like those seen in other lymphoid tissue were present. They were not coalescent, nor was necrosis marked; similar small focal lesions were present in the spleen; in all places fungi were found in the lesions peculiar to the disease.

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[1] LeCount, E. R.: Jour. Ment. Dis., 1908, xxxvi, 144.

A CASE OF SYSTEMIC BLASTOMYCOSIS

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CASE XXVII (9).—*History.*—S. C., an Italian laborer, aged 31, was admitted to the Cook County Hospital Jan. 11, 1909, to the service of Dr. Ormsby. Through an interpreter it was learned that he had been sick for three months. He suffers from persistent cough which is productive of a purulent, often blood-tinged, mucus. The appetite had been poor and emaciation rapid. Since the onset of his illness numerous cutaneous ulcers and subcutaneous abscesses have developed. He has had profuse night sweats and is now very weak.

Nothing could be learned of his previous illness. During the past year he lived with several other men in a small room under most unhygienic conditions.

Examination.—On examination the anemia and emaciation were quite pronounced. A number of cutaneous lesions were distributed over the body as follows: scalp and left eye, chin, back of neck, shoulder and forearm, right arm and thigh and right side of chest and back. These appeared to be ruptured pustules the site of which was healing and covered with a crust or extending, producing a characteristic papillomatous ulcer. Subcutaneous abscesses from 1 to 7 cm. in diameter existed beneath the skin of the scalp, above the right eye, left cheek and forearm, left thigh and right forearm. The left ankle was swollen and tender, especially over the internal malleolus. Motion was painful and walking difficult. The inguinal lymph-nodes were slightly enlarged. On examination of the chest impaired resonance with diminished transmission of breath- and voice-sounds were present over the apex of the right lung anteriorly and the base posteriorly. Both apices were dull on percussion posteriorly, and increased breath- and voice-sounds were heard. No râles were noted. Nothing of importance was found on further examination. A diagnosis of blastomycosis was made by Dr. Ormsby, who had seen the patient some time before, and this was corroborated by the demonstration of the organisms in the pus and also in the sputum. The pulse was 80, temperature 98.6 F., respirations 24. Although very weak the patient was able to get up and move about the ward. A high evening temperature developed in the next few days, and on January 19 the patient was compelled to remain in bed because of pain in the left ankle. An examination of the blood at this time showed white cells 8,600 per cubic centimeter, red cells 4,464,000, hemoglobin 72 per cent. Two days later the leukocytes numbered 10,800 per cubic millimeter. A differential count showed the following: polymorphonuclears 87 per cent., small mononuclears 2.35 per cent., large mononuclears 7 per cent., eosinophils 1.7 per cent., transitionals 1.1 per cent., myelocytes 0.6 per cent. An examination of the urine also was made but nothing abnormal found.

Treatment and Course.—The patient was given potassium iodid in doses from 15 to 90 grains per day during his stay in the hospital. Larger doses could not be given because of intolerance.

From January 23 to February 25 injections of vaccine prepared from the filtrate of old bouillon cultures of blastomycetes were given in doses varying from 2 to 10 minims. During this time the patient improved considerably; the pain in the ankle gradually subsided, the pulse and temperature became normal and several large abscesses were opened and began to heal. At this time 2 c.c. of the filtrate were given and was followed by a rise in temperature to 101 and an exacerbation of the local lesions. The temperature gradually decreased to 99.6 F., and on March 2 and 3 two more injections of 5 minims each were given followed by slight rise in temperature but no improvement. The injections were discontinued at this time. The temperature a few days later became irregular and high, rising at times to 103; new abscesses appeared and the old ones increased in size. The general condition gradually became worse and the cough increased in severity until April 11, when death occurred. During the last few days of the patient's illness a rigidity of the neck, slight strabismus, exaggerated reflexes, and a positive Babinski sign were noted.

Necropsy.—The post-mortem examination made April 11 concluded with the following anatomical diagnosis: chronic blastomycosis of the upper lobe of the left lung; erosion of the third and fourth thoracic vertebrae; blastomycotic abscess of the root of the right lung; disseminated miliary blastomycosis of the spleen and liver; blastomycotic basilar meningitis; abscesses of the prostate, peritonsillar tissues, epididymis, skin (with ulcers) and subcutaneous tissues; caries of the foot-bones; multiple intercostal, subpleural abscesses; blastomycotic tracheobronchial lymphadenitis. Fibrinous and fibrous pleuritis; fibrous peritonitis; emaciation and anemia; brown atrophy of the heart; atrophy of the liver; slight sclerosis of the aorta and coronaries; emphysema of the lungs; ossification of the thyroid cartilage.

Some parts of the description of these alterations are of considerable value in giving to the reader clear notions of the disease; this pertains especially to the description of the exterior of the body.

"The body is that of a much emaciated man with sunken abdomen. He measures 166 cm. in length. His hair is black and there is a sparse black beard. The ears are small and pinched. There are crusted lesions on the body and face as follows: over the right eye; on the bridge of the nose; the left eye including the lids; over the left zygomatic arch; on the chin in the median line; in front of the right ear and 2.5 cm. outside of the left angle of the mouth. The largest is that involving the left eye; this is the size of a half dollar; the next largest is that between the eyebrows; then in order are the lesions on the chin, the outer angle of the mouth and over the right eye. There are two lesions over the right ear covered by crusts. All lesions when pressed on exude a thick gray pus. A nodule is felt in the neck behind the right sternocleidomastoid the size of a walnut. There are dry crusted lesions at the posterior margin of this muscle, behind on the neck in the median line just below the spinous process of the first cervical vertebra, and two fingers' breadth below this, all the size of a dime. Fluctuation can be made out behind the mastoid process on the left side; the region involved is the size of the terminal phalanx of the thumb; it extends for two fingers below this and a little to the left. There is one small crusted ulcer on the back over the spine of the left scapula, a second one over the middle of the right scapula, and a third lesion opposite the third thoracic vertebra; a fourth occurs over the angle of the tenth rib on the left side. All these lesions are flat, little more than pigmented scaling spots. Many other lesions are present over the rest of the body. Of these eight are on the trunk, seven on the upper extremities and eight on the lower extremities. One of the latter just below the right knee is an abscess which has ruptured. The skin around it is covered by a brown crust; an incision into this demonstrates connection with an eroded bone. The abscess is oblong, 8 cm. long and lying along the outer aspect of the tibia. There is another lesion over the right thigh one hand's breadth below the anterior superior spine. It is 4 cm. across, circular in outline, elevated, fluctuates and the skin over it is not changed.

"The circumference of the trunk at the navel is 59 cm. The right arm may be spanned by the thumb and middle finger, as may also the legs. The right thigh in its middle measures 28 cm."

The alterations in the lungs were in many respects like those repeatedly noted. "The right lung weighs 555 gm. It floats well above the surface; it is mottled externally with brownish irregular spots which are a little sunken and most of which are 3 to 4 mm. in size. Deep in the fissure between the lower and upper lobes is a patch of greenish exudate the size of a finger-nail. The diaphragmatic surface is cupped and brown in color. The lung is crepitant throughout. The borders are pink and gray, a little rounded and elastic. In the main bronchus there is a mucopus, the lining is smooth and the pus is blood-stained. On section there is exposed near the root an abscess surrounded by dense tissue, the contents of which are the same as the other abscesses, a thick gray-green. The cavity is small and would admit an object the size of a pea. In the lower lobe a grayish region of consolidation is seen; this is elevated above the cut surface. It is 2 cm. long, has a grayish-yellow irregular margin and is located about the middle of the lobe. There are practically no changes in the remainder of the lung. The lung contains bright red blood. The left lung weighs 455 gm. On removal it is torn and the torn surface is twice the size of a dollar. There are adhesions at the apex where this torn region lay along the left side of the upper three thoracic vertebrae. On the whole the left lung externally is similar to the right. It is of a light feathery consistency and there are small, pea-sized flat black, firm elevations of coal deposits on the lower lobe in the fissure. In the region of the apex the lung is somewhat consolidated. On section the cut surface contains a good deal of bright red blood. The bronchi are like those of the right lung as regards their content. The lung under the torn region is dark and beset with minute pin-head-sized regions of softening. The region of consolidation about the torn apex is 10 cm. in diameter.

"There was a small abscess 3 mm. in diameter in the left lobe of the prostate. In the globus major of the left epididymis there was another small abscess."

More interesting than any of these were the changes in the brain and meninges and of these the following record was made: "There are two spots in the dura mater over the anterior portion of the left parietal lobe the size of a penny, and corresponding to them the bone is pink. Over the base of the brain there is a thick gray pus or fibrinopurulent exudate, thickest about the circle of Willis, where the chiasma and corpora mammillaria are completely hidden. This exudate extends out into the beginning of the Sylvian fissure back over the pons and medulla and for a distance equal to the width of two fingers. From these structures it gradually thins out on the inferior surface of the cerebellum. When sectioned horizontally there are exposed in the fundi of the sulci aggregated, and in places single, minute gray regions, some scarcely visible; others, especially on the right side, are so large and numerous as to form a marble-sized lesion. All of these deeper lesions are but extensions of the external process and in none of the sections made are there deeply placed focal lesions which require an embolism of fungi to explain their occurrence. The dura covering the basilar groove of the occipital bone is roughened for an area the size of a split pea; the bone beneath is unchanged." From the cerebrospinal fluid and from two of the subcutaneous abscesses the blastomycetes were recovered in pure culture. In cover-glass preparations of the purulent material used no bacteria were found. The peritoneal fluid and the blood of the heart proved to be sterile.

Histological Examination.—A careful examination of the various viscera failed to reveal any lesions in the internal organs other than those noted in the postmortem examination. The usual changes were demonstrable in the chronic blastomycosis of the left apex; the peritonsillar and prostatic abscesses, possessed walls similar to the subcutaneous abscesses. The abscess in the peritonsillar tissues in the sections examined apparently had not originated in the lymph-node, for the immediately adjacent tissue was striated muscle; nor did the sections support an origin in the tonsil. In the tracheobronchial lymph-nodes the lesions were small and in all other respects like those found in other cases. In the sections of the dura over the clivus of the occipital bone both fungi and giant-cells were found, but the minute focal lesions were pressed out flat and lay between or on the heavy fibers of the dura much like the similarly compressed "miliary abscesses" seen in the thickened pleura of other cases.

A CASE OF SYSTEMIC BLASTOMYCOSIS

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Case XXVIII (10).—*History.*—A. F., man, aged 19, entered the hospital April 15, 1909, to the service of Dr. Ormsby. He stated on admission that ten months ago he came from Bohemia where he lived on a farm, and has since worked as a tailor in a sweat-shop on the south side of Chicago. His illness began eight weeks ago at which time he coughed much, expectorating a mucopurulent material which often was tinged with blood. Three weeks later a small painful swelling developed on the back of the right hand. This has since increased in size, and fluctuation has developed. At about the same time a tenderness in the right testicle was experienced. On other parts of the body there developed successively a number of cutaneous and subcutaneous abscesses. The patient has lost about 20 pounds in weight since the onset and is at present very weak and is unable to work.

Examination.—Shortly after admission the temperature was normal, pulse 90, respirations 24. Emaciation was quite marked, and abscesses varying in diameter from ½ to 3 inches were distributed as follows on the forehead, two on the right side of the head and neck; one over the left deltoid region and one in the sixth rib; two on each arm; one in the left calf and one just above the heel on the same side. The left globus major was somewhat enlarged and quite tender. A slight dulness was noted over the right lung posteriorly, being more marked over the upper lobe, where occasional moist râles, harsh breath-sounds and increased vocal fremitus were heard. Prolonged expiratory breath-sounds over the apices were also found. The heart was normal in size and a soft systolic murmur was heard over a limited area at the apex.

The case was at once recognized as systemic blastomycosis and, as expected, many organisms were found in a smear made from pus aspirated from one of the abscesses. The organisms were also subsequently obtained in pure cultures.

In an examination of the sputum, which was bloody, no tubercle bacilli were found, but blastomycetes were abundant. These were also found in the sediment of several centrifuged specimens of urine which otherwise were normal. One week after admission the patient was anesthetized and all of the abscesses were evacuated and swabbed with tincture of iodin. The abscess of the back of the hand was found to be associated with necrosis of the third and fourth metacarpal bones and these lesions are quite evident in a roentgenogram taken at that time. Immediately after the operation the temperature, which previously had been normal, rose to 100.4 F., and this represented the high temperature for the next few days, during which time the patient complained of a pain in the back. April 25 a profuse nasal hemorrhage occurred. In order to determine whether this patient would react to the injection of a blastomycotic vaccine in a manner similar to other cases, 1 c.c. of a filtrate of bouillon culture of blastomycetes was injected subcutaneously, April 27. The temperature on previous days between 4 and 8 p. m. had been 100.4 F., associated with a pulse of 100, respiration 22. On the 28th, one day after the injection, the temperature was 100.6 F. at noon and at 4 p. m. was 102.6 F., pulse 108, respirations 24. On the following day the high temperature was again 100.4 F. and has remained at about this point. Increased pain or changes in local lesions were not noticed.

A differential count of the leukocytes made before the injection showed polymorphonuclears 68 per cent.; large mononuclears 17 per cent.; small mononuclears 13 per cent.; eosinophils 1 per cent. Another examination made May 3 resulted as follows: leukocytes 7,000 per cubic millimeter. Of these the polymorphonuclears constituted 62 per cent.; large mononuclears 13 per cent.; small mononuclears 22 per cent., and eosinophils 3 per cent. The hemoglobin by both Dare and Sahli-Gower instruments was 57 per cent.

Treatment.—Potassium iodid was administered in doses which were gradually increased to the extent that on May 3 the patient was receiving 70 grains three times a day. He was kept in the open air as much as possible and a nutritious diet given. In spite of this the patient seemed to grow weaker and on May 5 six new abscesses about an inch in diameter were found to have developed in the extremities, and the patient complained of pain in the back and left foot. In the latter a small, tender swelling about the second metatarsophalangeal junction was found. Roentgengrams were taken of this region and also of the right hand and the sixth rib, in which lesions existed as described.

On July 12, 1909, it was noted that the patient's general condition was somewhat less favorable. A number of abscesses had healed and new ones had occurred as follows: one over the right scapula; one in the right forearm just above the wrist; one in the left arm, and one under the right eye. The right shoulder was very painful and on close examination the acromial process of the scapula was found to be involved to the extent that displacement was possible. The right thigh also was very painful, but no superficial abscess could be found. The lungs were involved to a greater extent than before, but no other visceral changes were noted. From this time the patient grew gradually weaker and many new abscesses appeared. Death occurred December 13. The necropsy report is as follows:

Necropsy.—The body is that of a young adult white male, 158 cm. in length, considerably emaciated. The hair in the back of the scalp is worn off. On the left side of the forehead near the hair-line is a small triangular scar 2 cm. in diameter. The eyes are sunken. The facial muscles are atrophied. Just below the left orbit is a superficial skin lesion, about 1.5 cm. in length, slightly elevated and crusted. A similar lesion, somewhat hemorrhagic, is present near the right ala of the nose.

Just above the tip of the left shoulder is an ulcerating skin lesion measuring 5 by 3.5 cm. The margins are purplish, contain scar tissue and are slightly elevated; the floor of the ulcer consists of the ligaments of the shoulder-joint, and an area about 1 by 2 cm. seems to connect with the shoulder joint. The anterior aspect of the left shoulder shows a soft, egg-shaped swelling 2 cm. high which fluctuates. On the right arm half way between elbow and shoulder on the lateral aspect is an ulcer measuring about 4 by 5 cm. The margins are scarcely raised, and in the floor exposed muscular tissue may be seen. The right elbow can be extended to an angle of about 120 degrees; crepitus is felt; a soft fluctuating mass is present on the posterior surface just above the olecranon. On the volar surface of the right forearm about 5 cm. below the elbow is an elongated pigmented scar. A few other small scars appear lower down on the forearm. Motion of the wrist is much restricted in all directions, and crepitus can be felt and heard. On the back of the right hand, over the middle metacarpal is an ulcerated area about 1 by 3 cm., communicating with the subcutaneous and interosseous tissue, and on pressure a small amount of mucoid yellowish material can be expressed. About the base of the first metacarpal, a purple fluctuating area may be felt. On the radial aspect of the left forearm about 6 cm. below the elbow is a crusted skin lesion about 2 by 0.5 cm.

Posteriorly just above the spine of the right scapula is a skin lesion about 1.5 cm. in diameter communicating with the deeper tissue, from which a small amount of yellowish mucoid material can be expressed. Just below the level of the twelfth rib at the right of the spine are two small fistulous openings in the skin surrounded by a purple areola, from which a small amount of necrotic material can be expressed. On the right side, about 1 cm. above the level of the iliac crest is a small ulcerated lesion from which a yellowish cloudy liquid escapes. Over the sacrum is a large decubital ulcer measuring 12 by 4 cm. Both hips are ankylosed in a semiflexed position, and in the left hip crepitus is evident.

A muscular contracture holds both knees in a semiflexed position. About the right knee on the anterior surface are many areas of cicatrical tissue of varying sizes. Just above the left patella is a superficial skin lesion measuring 4 by 2 cm. covered by thin papery scales of epidermis. Near this and to the left of it is a similar lesion about 1 cm. in diameter. On the anterolateral aspect of the left leg about 15 cm. below the knee is a small superficial ulcer. The anterior borders of both tibiae are very sharp and somewhat curved laterally. The left foot, especially on the dorsum, is swollen and puffy. Between the first and second toes of the left foot is a ragged ulcer about 1 cm. in diameter from which grumous material can be expressed.

When the abdominal cavity is opened, the peritoneum is smooth and shining. The omentum is devoid of fat, and is rolled up transversely. The lower border of the liver lies about one finger's breadth above the costal margin in the mammary line. The appendix lies over the brim of the pelvis; it is about 5 cm. in length, is free from adhesions and appears normal. It has a mesentery of its own for its entire length.

The right pleural cavity has posteriorly and laterally a considerable number of easily broken adhesions. The lung is also somewhat adherent to the diaphragm. This cavity contains no fluid. The left pleural cavity is free from adhesions and fluid, except at the level of the fifth rib, where it is firmly adherent to the chest wall. At the site of this adhesion, the fifth rib for a distance of about 2 cm. is considerably eroded, the osseous tissue being practically absent.

When the pericardial cavity is opened, the pericardium is smooth and shining, and contains a small amount of free fluid. The heart is rather small. On the anterior surface of the right ventricle is an area about 1 by 2 cm. which is light in color, slightly elevated, and somewhat thickened. The mitral orifice admits the tips of two fingers. The left ventricle is firmly contracted. The musculature is rather pale. The wall measures 15 mm. The mitral valve is normal in appearance. The foramen ovale is closed. The aortic orifice admits one finger readily. The aortic leaflets are normal in appearance, as is also the base of the aorta. The tricuspid valve appears normal, as do the pulmonary artery and pulmonic valve. The area referred to on the anterior wall of the right ventricle is confined chiefly to the pericardium, but a small whitish area extends into the musculature. The weight of the heart is 200 gm.

The spleen weighs 200 gm. It is somewhat enlarged; the surface is smooth; the consistency is firm. Near the upper pole on the anterior and lateral surface is a slight constriction marking off a small lobule. The surface is purplish; the capsule strips with difficulty. On section, the color is redder than usual; the markings are fairly distinct.

The tongue, trachea and esophagus appear normal.

The right lung weighs 450 gm. The lung collapses somewhat; it crepitates feebly. It shows evidences of fibrous adhesions on all except the anterior surface. The upper lobe feels firm, but no small nodules can be felt. On section the lung is light red; on pressure a small amount of frothy fluid can be expressed. At the base of the upper lobe is an area which is firm, dark purple and airless. On pressure, no fluid escapes from the alveoli, but a small amount of purulent material from the mouths of the smaller bronchi. At the upper edge of this area is a pea-sized cavity containing a small amount of yellow mucoid material. The left lung weighs 400 gm. The surface is free from adhesions except at the base, and at the lower margin of the upper lobe Very little crepitation is felt. On section, the lung is light in color, and on pressure a very slight amount of frothy fluid may be expressed.

The pancreas is normal in appearance and consistency except that the lobules are rather poorly marked. On section it shows no pathological change.

The liver with the gall-bladder weighs 1,700 gm. The gall-bladder contains a moderate amount of dark bile and no stones. The surface of the liver is smooth; its color is mottled pinkish. On section the color is a rather muddy yellowish-brown, the markings are fairly distinct; on pressure a small amount of bloody fluid is expressed.

The stomach is about normal in size. The rugae are well marked. The mucosa appears normal.

The kidneys together weigh 450 gm. The left kidney is the larger of the two. The surface is pink, and is somewhat irregular. The cut edges do not bulge. The capsule strips readily. The color is pale. The ratio of cortex to medulla is 12 : 18. The markings are indistinct. The right kidney is smaller, but otherwise corresponds to the description of the left.

At the level of the fourth lumbar vertebra on both sides are found abscesses. On the right side the abscess has burrowed laterally about 9 cm. beneath the posterior abdominal wall. Inferiorly, it has burrowed far below Poupart's ligament. On the left side the abscess has burrowed laterally but a short distance. Inferiorly it has burrowed far below Poupart's ligament. Both abscesses have pointed posteriorly. The right side of the body of the fourth lumbar vertebra is somewhat roughened. On chiseling into it, an abscess cavity is encountered which occupies about one-third of the body of the vertebra. It contains a yellow mucoid material. The third and fifth lumbar vertebrae show no gross lesions. The cartilage between the fourth and fifth lumbar vertebrae is quite soft.

The large intestine is negative. The lower portion of the ilium shows a number of small congested areas, but otherwise no change.

Anatomical Diagnosis.—Generalized blastomycosis involving skin and subcutaneous tissue in many regions, left shoulder, right elbow, right wrist, left hip, fourth lumbar vertebra, right lung and left fifth rib; adhesive pleuritis—bilateral; passive congestion of liver; acute splenitis; chronic parenchymatous nephritis; bilateral psoas abscesses (blastomycotic); consolidation at base of right upper lobe with small abscess (blastomycotic).

Blastomycetes were recovered in pure culture from the cavity in the right lung, and were found in smears of the pus from all of the abscesses, but only in the lung were they numerous. The smears were examined for tubercle bacilli, but none were found. The microscopical examination of the tissues will be reported later.

A CASE OF SYSTEMIC BLASTOMYCOSIS

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CASE XXIX (11).—*History.*—J. D., aged 30, Hungarian, has resided in this country for about two years and speaks no English. He was first employed in West Pullman, Ill., for a short time, working in a foundry. He next worked in the car shops, assorting and piling on trucks the various kinds of wood. Patient declares that his hygienic conditions have always been good (good ventilation, no dampness, etc.) and that he has slept alone in a room which he describes as being dry and large enough for two beds. There is no history of any other occupant of the house having had the same trouble as his.

Patient dates his illness from Oct. 1, 1909. Illness started with a bad cold, a severe cough and pain in left side. He does not know if he had fever. Three weeks later he began to cough up blood, at times in large amounts, and he has continued to have bloody expectorations daily, two or three in number, since then. He became dyspneic shortly after the onset of his cough. He does not know how much weight he has lost but says he weighed 160 pounds at one time before his illness started. At present he weighs about 110 or 120 pounds. He has had no night sweats and thinks he has had no fever whatever during his sickness. His appetite has been good. No history of bloody or abnormal number of stools can be obtained. Patient states he has not vomited or suffered any epigastric discomfort. There has been no pain on urination, but he complains of a constant pain in the back which has been so severe as to incapacitate him, and at times keep him from sleeping. Coughing has now ceased for the past two weeks.

About six weeks ago the present lesion over the right eye appeared. A few days later a second similar lesion was noted over the left eye. These were followed in rapid succession by numerous abscesses elsewhere on the face, extremities and trunk, and were accompanied by the usual signs and symptoms of any ordinary localized skin infection. He has been getting weaker all the time and now is unable even to sit up in bed.

The patient entered the Cook County Hospital Dec. 2, 1909, and was admitted to the Tuberculosis Hospital with the diagnosis of pulmonary tuberculosis. It was while there that he developed the skin lesions which aroused the curiosity of the intern, who consulted Dr. O. S. Ormsby as to their nature. The latter made a diagnosis of systemic blastomycosis and patient was transferred to the Skin and Venereal Ward on Dr. Ormsby's service. While he was at the Tuberculosis Hospital, three sputum examinations were made for the presence of the tubercle bacilli but with negative results.

The man's family history throws no light on the etiology. He is married and has two children living and well. Patient drinks several whiskies and about one pint of beer daily. Smokes moderately. Had gonorrhea five years ago. Three years ago he was ill for eight months with a disease of unknown nature. He says that he felt weak, coughed, had no night sweats, and lost little weight. At this time he had no skin lesions of any sort.

Examination.—Physical examination, March 5, 1910, elicited the following: The patient is very much emaciated, highly anemic with a lemon tint to skin; he appears very ill, and is too weak to move about. No cyanosis or dyspnea. No edema of extremities, etc.

Multiple abscesses are scattered diffusely over body. These are of two types: Those of the face and scalp are crusted, globular, about the size of a large hickorynut, brownish-red and surrounded by a slight inflammatory zone. Some have ruptured, and exude a thick yellowish mucoid material. These lesions are scattered diffusely about the face and scalp. Those of skin of extremities and trunk are not crusted; the overlying skin is but slightly inflamed even in the case of the large abscesses and those of great tension. All are painful on pressure and prevent the patient from moving about. Anteriorly on the chest wall over the seventh rib at its junction to the sternum is a small fluctuating abscess apparently connected with that rib. Likewise an abscess over the region of the sixth dorsal vertebra appears to have communication with the lateral process of that vertebra.

The tongue is badly coated; there is moderate pyorrhea alveolaris; the breath is foul and heavy; tonsils moderately enlarged. A large submaxillary lymph-node about the size of a small hen's egg exists on the left side of the neck; it fluctuates and is tense.

Litten's sign is absent on right side of the chest. There is marked emaciation of chest wall with depression of superclavicular spaces. Motion is restricted in both sides.

Dulness is obtained on the left side posteriorly over lower part of upper lobe and entire lower lobe, and also impaired resonance of right apex, and over entire left lung anteriorly.

Bronchial breathing with fine crepitant râles, increased vocal and tactile fremitus, and exaggerated whispered sounds are noted over the dull area posteriorly on the left side. Mucous clicks are heard over the left lower lobe posteriorly.

Anteriorly a few râles are heard in both axillae, and also fine crepitant râles in both apices. The râles of the dull area on the left side are few in number — the breath-sounds are harsh and roughened with a moderate prolongation of the expiratory murmur. The findings on percussion suggest an advanced pulmonary tuberculosis, while the auscultatory findings would indicate an incipient stage of the disease. No signs of abscess cavity can be elicited. The heart is enlarged a little to the left, and on auscultation an apical systolic murmur can be heard.

The pulse is small in volume and moderate in tension, with a tendency toward dicrotism.

The spleen, liver and kidneys are not palpable.

Except for some adenopathy of the inguinal lymph-nodes, further examiation was negative.

The patient's temperature ranged from 98.4 to 103.4 F., with periods of normal temperature for days at a time. No characteristic evening rise or morning subnormal temperature is recorded.

The respiratory rate varied from 20 to 36 according to the temperature.

The pulse-rate ranged from 86 to 110.

Urine: Specific gravity 1.020; acid; cloudy and amber-colored; no albumin; no sugar. Microscopical: Few hyalin casts; few leukocytes; many urates and phosphates; no blood microscopically or chemically.

No blastomycetes were found in the urine on repeated examination.

Blood: Hemoglobin 48 per cent. (Dare and Sahli); erythrocytes 1,600,000; color index 1.46 +; white cells 22,000. Differential count: polymorphonuclear neutrophils 86 per cent., eosinophils 1 per cent., mononuclears, large 9 per cent., small 4 per cent., moderate poikilocytosis.

Blood-cultures were negative.

Sputum was negative for tubercle bacilli and blastomycetes.

Feces: Negative for blood (Weber).

The Wassermann test was kindly made by Dr. J. H. Waugh, and was negative.

A subcutaneous injection of tuberculin (Koch's old), 0.02 mg., was given, increasing 0.04 mg. each dose for three successive doses at intervals of three days. This was done during the period of apyrexia — after the last dose, the temperature was 101 + F. and remained about the same for the following few days, when it again became normal. Because of the irregular temperature curve, little importance as to the presence or absence of tuberculosis can be attached to the results.

A direct smear from one of the intact abscesses mounted in 20 per cent. potassium hydroxid showed the characteristic morphology of the blastomycetes — budding forms, etc. Cultures from two skin lesions showed the organism in pure culture.

In summarizing it is noted that this case resembles pulmonary tuberculosis in the following: onset with cough, hemoptysis, loss of weight and strength, marked emaciation, lung findings.

In this regard it is noted that the auscultatory findings are insignificant as contrasted with those elicited on percussion, namely, an area of greatly impaired resonance will give few or no râles, etc.

MULTIPLE PRIMARY MALIGNANT TUMORS

WITH A REPORT OF TWO CASES IN DOGS *

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Multiple primary malignant tumors occurring in the same individual are comparatively rare. Götting[1] in over a thousand necropsies on malignant growths encountered only two cases; von Hansemann[2] in the same number of necropsies found five; Redlich[2] in 507 cases had two; Reichmann[2] in 711 cases also had two. Several writers look on these sporadic cases as purely accidental, while others, as Adami,[3] Wooley[4] and Williams,[5] attach considerable importance to them, especially in the further consideration of the nature and etiology of malignant tumors.

In the vast majority of cases, single malignant tumors originate from a single type of tissue, that is (for example), the squamous epithelium, the low cuboidal cells of the mammary acini, or the connective tissue. Malignant tumors are rarely composed primarily of both a transformed epithelium and of a transformed mesoderm. Until 1901, Wells[6] found but three undoubted cases of this type, including his own case, the so-called sarcocarcinomas, all of which had developed from the thyroid gland. In Wells' case the primary tumor was a mixture of a carcinoma with a sarcomatous stroma, giving metastases of pure carcinoma, of pure sarcoma, and of a mixture of both. Herxheimer,[7] in 1908, collected from the literature reports of twenty cases of carcinosarcomatodes occurring in man. There are many cases of this sort of tumor reported in the literature that are not true carcinosarcomatodes, but are mixtures of two entirely

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[1] Götting, H.: Zur Multiplizitat primärer Carcinome, Ztschr. f. Krebsforsch., 1908-1909, viii, 675.

[2] Quoted by Götting. (See Footnote 1.)

[3] Adami, J. G.: Concerning the Causation of Cancerous and Other New Growths, Yale Med. Jour., 1901, vii, 309 and 343.

[4] Wooley, P. G.: Notes on Multiple Primary Tumors, Boston Med. and Surg. Jour., 1903, cxlviii, 1.

[5] Williams, R.: Bilateral Tumors — Malignant and Non-Malignant, Lancet, London, Feb. 1, 1910, p. 426.

[6] Wells, H. G.: Multiple Primary Malignant Tumors, Etc., Jour. Path. and Bacteriol, June, 1901, p. 357.

[7] Herxeimer, G.: Ueber das Carcinoma Sarcomatodes und einer einschlägigen Fall des Oesophagus, Beitr. z. path. Anat. u. z. allg. Path., 1908, xliv, 150.

separate tumors, namely, a sarcoma and a carcinoma, each having originated separately and later having so thoroughly mixed with one another as to give the appearance of a tumor of single origin. Such a case is reported by Spencer,[8] in which a sarcoma and adenocarcinoma occur close together in the uterus, in places mixed, resembling a true sarcocarcinoma. Closely allied is the case reported by Schöne,[9] in which there is in the thyroid both a sarcoma and a carcinoma, closely approximated, yet quite distinct from each other. Nebesky's[10] case of a spindle-cell sarcoma of the uterus together with a papillary adenocarcinoma adjacent to it exemplifies a similar condition. Some of these cases, then, are indistinctly separated multiple primary malignant tumors.

It is interesting in this connection to point out that Ehrlich and Apolant,[11] by inoculating a typical adenocarcinoma through ten generations of mice, finally obtained a mixed tumor, the stroma of which was a spindle-cell sarcoma. By the thirteenth generation, all traces of the original carcinoma tissue had disappeared, leaving a sarcoma which as late as the twenty-sixth generation was still a typical sarcoma. Sticker[12] reports a similar experience; he inoculated a spindle-cell sarcoma into the mammary gland of a dog. This resulted in the formation of a typical mammary carcinoma. Like results have been reported by Lewin and by Loeb. According to Ewing, in discussing the case of Ehrlich and Apolant, there are four possibilities: first, there is a transformation of epithelial cells into the sarcomatous-appearing cells; second, there is a sarcomatous element in the original tissue; third, the stroma of the original tumor has become malignant, and fourth, the stroma of the host has become malignant.

It is the general conception at present that any one malignant tumor originates from one single primary focus, or in other words, that it is monocentric. Peterson, however, from the study of serial sections of early malignant tumors, believes that a pluricentric origin is the rule rather than the exception. Wooley[4] reports a case of carcinoma of both adrenals in which there are in all five primary foci of similar histological structure. The proximity of these foci, three being in one adrenal, supports Peterson's stand, and makes it plausible that foci still more closely set would at a later stage in the growth of the tumor be conglomerate

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8. Spencer, H. R.: Carcinosarcoma Uteri. Tr. Obst. Soc., London, 1905, xlvii, 235.

9. Schöne, G.: Sarkom und Karzinom in einer Schilddrüse beim Hunde. Virchows Arch. f. path. Anat., 1909, xix, 169.

10. Nebesky: Arch. f. Gynäk, 1904, lxxiii, 653.

11. Ehrlich, P., and Apolant, H.: Zur Kenntnis der Sarkomentwicklung bei Cacinom Transplantation. Centralbl. f. allg. Path. u. path. Anat., 1906, xvii, 513.

12. Sticker, A.: Experimentele Erzeugung des Carcinoms beim Hunde, Arch. f. klin. Chir., 1909, xc, 577.

and would obscure its multicentric origin. From the study of very early basal-cell carcinomas, for example, one is impressed by the diffuse area of cells, apparently all primarily on the road to malignancy. In discussing his case of multiple primary carcinomas of the adrenal gland, Wooley states that the adrenal cells surrounding the small primary carcinoma foci appear to be undergoing malignant transformation; he suggests that all the normal cells about these foci are unbalanced and are tending toward malignancy. It is, of course, impossible to determine in tumors beyond their early growth whether or not their initial impetus was from a monocentric or pluricentric origin. One cannot exclude entirely the possibility of a local predisposition, which in a broader interpretation indicates the susceptibility of a certain tissue, that is, the skin, or fascia, or even a system of tissue including, for instance, the mammae, the ovaries, the uterus and the tubes. Thiersch,[13] Adami, Bucher,[14] Warthin,[15] Wooley and others have mentioned local predisposition or susceptibility, in explanation of the occurrence of distinctly separated, though closely seated, primary malignant tumors.

The fact that multiple primary malignant tumors are often bilateral and symmetrical is significant perhaps in many cases of a predisposition on the part of the tissue affected. This predisposition, Williams believes, is a developmental disturbance. A great many instances supporting this view are to be found in the literature. Zangemeister[16] found that out of thirty-nine sarcomas of the ovaries, ten were primarily bilateral. Pick[17] found nine bilateral primary sarcomas out of a series of twenty-three cases of sarcomas of the ovaries. Schubert[18] found three primary bilateral malignant testicular tumors out of a series of fifteen cases of malignant tumors of the testicle. In a series of 114 similar cases, Kober[19] found five bilateral instances. Williams points out that these malignant tumors of the testicle and ovary are more apt to be bilateral when the malignancy has developed early, and in view of this fact connects them with some developmental anomaly. Ladinskie[20] describes a case of sarcoma of one ovary and of a carcinoma of the other ovary in a woman

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13. Thiersch: Quoted by Warthin (see Footnote 15).

14. Bucher: Quoted by Warthin (see Footnote 15).

15. Warthin, A. S.: Multiple Primary Carcinoma, Jour. Am. Med. Assn., 1899, xxxii, 963.

16. Zangemeister, D. W.: Ueber Sarkome des Ovariums, Beitr. z. klin. Chir., 1896, xvi, 397.

17. Pick, L.: Zur Symptomatologie und Prognose der Sarkome des Eierstocks, Centralbl. f. Gynäk., 1894, xviii, 940.

18. Schubert: Quoted by Williams, W. R.: Natural History of Cancer, New York, William Wood & Co., 1908.

19. Kober, G. M.: Sarcoma of the Testicle: Conclusions Based on One Hundred and Fourteen Cases, Am. Jour. Med. Sc., 1899, cxvii, 535.

20. Ladinskie, L. J.: Absence of the Uterus and Vagina with Sarcoma of One Ovary and Adenocarcinoma of the Other, Am. Jour Obst., 1898, xxxviii, 78.

in whom both fallopian tubes and the uterus were congenitally absent. In this case anomalous embryonal growth is quite conclusively associated with the development of the bilateral malignancy. Rolleston and Marks,[21] out of twenty-six cases of malignant diseases of the adrenals, found that two cases were primarily bilateral. Walker[22] found ten primary bilateral malignant tumors out of a series of 141 cases of malignant disease of the kidneys. Kuster,[23] in the review of 607 primary malignant tumors of the kidney, found that there were thirteen primarily bilateral. A very remarkable case is cited by Newton,[24] in which ten children out of a family of sixteen died of glioma of the retina before they had attained the age of 5 years. Of these ten cases, seven were bilateral. It is seen from the foregoing instances, which are representative only of a class of cases, that multiple primary malignant tumors may occur in paired organs, and that the percentage of such cases is too high to be considered an incidental occurrence. These cases seem to indicate that a certain type of tissue may be predisposed to malignant transformation under favorable circumstances of irritation. They indicate some anomaly in the embryonal development of that particular set of organs.

Excluding bilateral primary malignant tumors of the ovaries, testicles, kidneys and adrenals, and also the sarcocarcinomas, I have reviewed reports of ninety-five cases of multiple primary malignant tumors; among these ninety-five cases are included the list reviewed by Williams, by Wooley and by Wells. In thirty of the ninety-five cases, there is no predilection for any particular system or type of tissue; twenty-seven of these thirty cases are represented by both a carcinoma and a sarcoma, while the remaining three cases are represented by only one type of malignant tumor. Thirty-four of the ninety-five cases occur in the reproductive system; the mammae, the ovaries, the uterus, the tubes and the vagina are included under this head; only one case in the male is reported. Of these thirty-four cases, sixteen are represented by both a sarcoma and a carcinoma, while in eighteen of the thirty-four cases only one type of malignant tumor is present, that is, either a sarcoma or a carcinoma. Thirteen of the ninety-five cases occur in the cutaneous tissue; two of these are each represented by a sarcoma and a carcinoma, while the remaining eleven are all represented by carcinomas. Again, thirteen of the ninety-five cases occur in the gastro-intestinal tract, including the esophagus, the stomach, the intestines, the liver and the pancreas. Of these thirteen cases, four are represented by two types of tumors, namely, a sarcoma and a carcinoma, while the remaining nine cases are represented by but one type of malignant tumor. There are three cases of multiple primary malignant tumors in bones, one case in the central nervous system, and one case in the glands of internal secretion. In all ninety-five cases there are but four instances wherein more than two primary malignant tumors occur in the same individual.

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[21] Rolleston, H. D., and Marks, H. W. J.: Primary Malignant Disease of the Suprarenal Bodies, Am. Jour. Med. Sc., 1898, ii, 383.

[22] Walker, G.: Sarcoma of the Kidney in Children, Etc., Ann. Surg., 1898, xxvi, 529.

[23] Kuster: Ueber Neubildungen der Niere und ihre Behandlung, Centralbl. f. d. Krankh. d. Harn. u. sex. Org., 1897, viii, 583.

[24] Newton, R. E.: Glioma of Retina, Australasian Med. Gaz., 1902, x, 236.

Briefly, then, it is evident that two-thirds of all these cases of multiple primary malignant tumors are confined to systems, while but one-third of the cases are miscellaneously distributed. A comparison may be drawn between the foregoing distribution of multiple malignant tumors and the multiple benign tumors, especially the subcutaneous neurofibromas, lipomas, ecchondromas and fibromas, the occurrence of which undoubtedly indicates some predisposition on the part of the tissue involved. We know that each of these multiple benign tumors is primary, because metastatic distribution can be ruled out. The oft-repeated statement can be reiterated here that "no sharp line of division is possible between the benign tumors and the malignant tumors." This fact, together with the foregoing statistics, indicates and indirectly confirms that multiple primary malignant tumors are, in certain cases at least, due to the existence of some susceptibility on the part of the tissue or system of tissues involved. Adami points out that in the female the involution of all the reproductive tissues at the climacteric is in some way connected with the very frequent occurrence of multiple tumors in this particular system. Williams believes that since the female reproductive system attains physiological maturity earlier than the rest of the body, its chances to develop malignancy are greater.

The type of malignant growth, as seen from the before-mentioned cases, is not so highly important in the consideration of multiple primary malignant tumors as is the system or tissue in which these tumors occur. Many factors, such as irritation, misplaced embryonal rests, climacteric and senile involution, parasites or infection may be involved in the lighting up of these system tumors. But behind these indirect causes which, boiled down, mean "irritation," there is, as far as can be determined, something else which in the interpretation of to-day is called a "biologic" disturbance.

This biologic disturbance may lead to a local, to a tissue, to a system, or to a general predisposition to malignant tumor growth. The recent work of Miss Sleye[25] at the University of Chicago in collaboration with Dr. Wells, has been the most extensive research yet done on experimental heredity of cancer in mice. Their work goes to show that an infective focus of long standing is much more apt to produce a malignant tumor in a cancerous strain of mice than in a non-cancerous strain; in the latter, an infective nodule, or perhaps a benign tumor, instead of a beginning malignant focus, may result from such an irritation. They further point out that multiple primary malignant tumors are much more frequent in these cancerous strains of mice than in the noncancerous strains. A sarcoma is as apt to crop out in these mice as is a carcinoma. It appears that in the cancer strains there is a definite hereditary predisposition and that this predisposition is general, including all types of tissue and all parts of the body. The best workers in the field of heredity in human cancer have so far failed to find any definite proof of a hereditary predisposition to malignancy.

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[25] Sleye, M.: Statistics to be published later.

CASE-REPORTS

The two cases of multiple primary malignant growths reported below occurred in Dogs A and B, both of which were brought to the laboratory for ordinary class-work:

Case 1.—Dog A. is an old male dog, weighing approximately 60 pounds. In an attempt to insert a tracheal cannula, a large diffusely infiltrating and very vascular growth was encountered in the region of the thyroid (Fig. 1).

Thyroid: The thyroid is firmly embedded in the surrounding soft tissues almost completely encircling the trachea, but not being adherent to or penetrating the latter. In places an irregular thin capsule is present, but it is not defining to the tumor mass. The tumor, which is very irregular, is 13 cm. long and 9 cm. wide, the larger portion lying on the right side. The large veins coursing over and leaving the tumor are almost all filled with papillous, worm-like tumor thrombi, some of which attain a length of 5 cm. The regional lymph-nodes are not involved by metastases, though on the left side two or three are incorporated in the tumor mass.

The cut surface of the tumor is very fibrous with soft centers or nests of cells in it. In places where the stroma is scarce, the tumor is soft and grossly like a small round-cell sarcoma. In either side is a small, necrotic and old hemorrhagic region.

Lungs: The lungs are the seat of numerous whitish-gray nodules, spherical in outline. They range from 1 mm. to 2 cm. in diameter and are about eighty in number.

Mediastinum: In the anterior mediastinum there is a nodule the size of a pigeon-egg, pedunculated and encapsulated. Two-thirds of it is gelatinous; the remainder is solid.

Adrenals: The right adrenal is replaced by a slightly irregular spherical tumor, 5.5 cm. in diameter (Fig. 2). It is surrounded by a thin fibrous capsule in which there are a few small veins. The color through the capsule is distinctly a dirty yellow and brown, quite similar to the ordinary renal hypernephroma. It is distinctly separated from the right kidney by a distance of 1.5 cm. At its inner border there is a nodule, 0.5 cm. in diameter, protruding from it, for a distance of 0.7 cm. The whole tumor is easily enucleated from the surrounding tissue. This adrenal tumor was cut into sagittal sections, 0.7 cm. apart. The section through the center reveals a surface that is for the most part necrotic, although it is rather firm. It is brownish-gray with irregular streaks of yellow through it; at the edges the mottling is of a bright reddish-brown as though from fresh hemorrhages. At the lower inner pole of the tumor, included within the capsule yet separated from the rest of the mass by a thin fibrous septum, is a crescent-shaped peripheral cap of tissue, 0.7 cm. thick and 4.5 cm. long. This is yellow and solid; it is quite unlike the rest of the cut surface. Other surfaces made by the sagittal sections reveal a similar condition, as just described, except that near the surface of the tumor the necrotic appearance fades and the yellow tissue, mottled with red, is in preponderance.

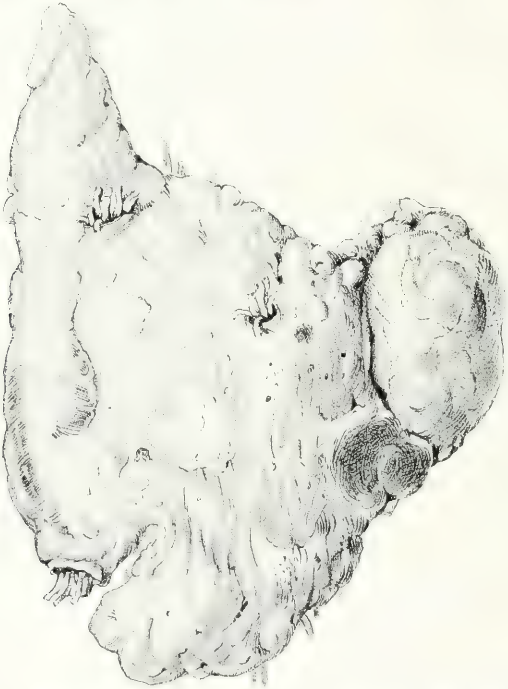

Fig. 1.—(Two-thirds natural size.)—Dog A. Carcinoma of the thyroid. The large veins coursing over and leaving the tumor are numerous and full of papillomatous tumor thrombi. The capsule is thin and ill defining.

The left adrenal is replaced by a spherical tumor 4 cm. in diameter, surrounded by a thin capsule and entirely separated from the kidney (Fig. 2). It is easily enucleated from the surrounding tissue. It is separated from the right adrenal tumor by a space of 4 cm., and no connection between the two is visible grossly. This tumor is a little firmer than the right one. On surfaces made by sectioning, it is seen to be beset throughout by small whirls of yellowish tissue, similar to adrenal cortex in color. These whirls range from 1 mm. to 1.5 cm. in diameter. The largest ones are seminecrotic.

Kidneys: Both kidneys are of the congenital multicystic type, the cysts being very numerous throughout both kidneys and ranging from 1 mm. to 3 cm. in diameter (Fig. 2).

Liver: The liver is normal except for a small 1.5 cm. cavernous hemangioma.

General: The rest of the body on careful examination reveals nothing of importance in connection with these tumors.

Microscopic: All the microscopical sections are stained with hematoxylin and eosin.

Dog A: Sections examined from various places in the thyroid reveal an adenocarcinoma, the alveoli of which are well formed in places and contain colloid. The majority of the alveoli are irregular, incomplete and without colloid. In the regions in which alveoli are present, the stroma is thick and fibrous. In the softer and non-fibrous portions of the tumor, the microscopic picture is that of a carcinoma simplex: the solid masses here are composed of cells with a small round nucleus, quite granular with chromatin and deep staining with hematoxylin. The cells are very indefinitely outlined, there being a few pink-staining plasma shreds and granules between the nuclei. In these softer regions the stroma is delicate with blood-vessels running through it. Still other regions of the tumor that are most fibrous to the gross examination are composed of almost solid hyalin connective-tissue masses with single cells, chains and irregular groups of carcinoma cells scattered throughout.

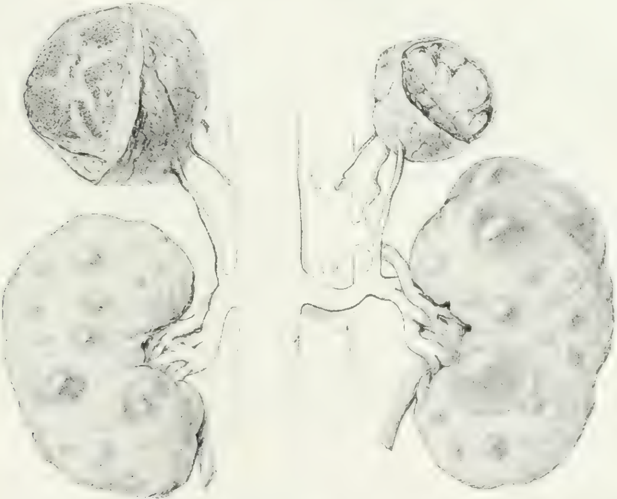

Fig. 2.—(Two-thirds natural size.)—Dog A. Bilateral congenital cystic kidneys associated with bilateral primary adrenal hypernephromas. The right adrenal tumor, with the exception of the subcapsular region, is almost entirely necrotic, with multiple regions of hemorrhage. The left tumor is composed of whorls of tumor tissue, set in a connective-tissue stroma; the large whorls are necrotic.

Lungs: All the tumor nodules in the lungs are of thyroid tissue, as is the pedunculated nodule in the anterior mediastinum, and also a small nodule accidentally discovered in the region of the pineal body. In the lungs the small nodules are in the blood-vessels; some are necrotic, while others, especially the larger ones, have a fibrous and vascular stroma. Most of the metastases tend to reproduce the same type of carcinoma tissue as was described in the thyroid tumor; some are adenocarcinomatous, while others are more of the carcinoma simplex type.

Adrenals: The microscopic picture is the same for both adrenal tumors, except that more necrosis is present in the sections taken from the tumor on the right side. The capsule is thick and fibrous, yet very irregular in its thickness. In either tumor the picture varies considerably in different places. For the most part, the central portion of both tumors is represented by a large polygonal cell, having a distinct bladder-like, yet often solid nucleus, and a cytoplasm distinctly outlined and vacuoled (Fig. 3). These cells are quite similar to the ordinary foamy cells in hypernephromas of the kidney. They are arranged in single and double cords, in nests, or set singly in a hyaline-like connective-tissue stroma. Between the columns and cords are great numbers of blood-sinuses; in fact, in places the dilated blood-sinuses have crowded and necrosed the tumor-cells.

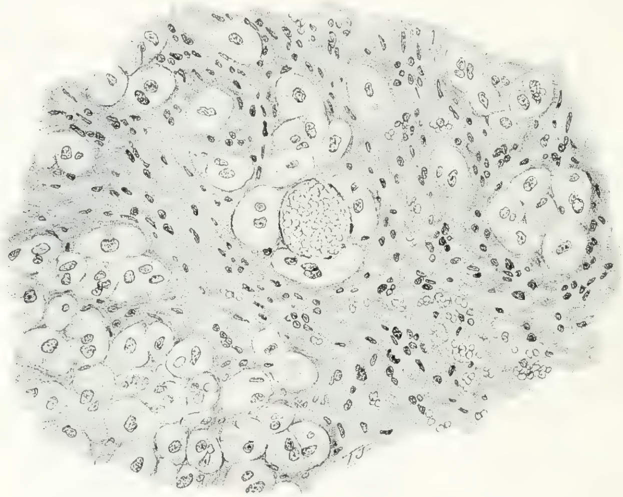

Fig. 3.—Dog A. Central portion of adrenal tumor, represented by a large polygonal cell, having a distinct bladder-like yet often solid nucleus, and a cytoplasm distinctly vacuoled. These cells are arranged in single and in double cordons, in nests, or set singly in a hyaline connective-tissue stroma.

In other places, smaller cells with a deeper-staining nucleus and a less defined cytoplasm are found in large masses. Between the cells a very delicate, embryonal connective-tissue stroma is found. This type of formation is mixed rather thoroughly in places with regions of the above-described foamy cells.

Just under the capsule in places is found an atypical zona fasciculata; these cells sometimes become sarcomatous in appearance, approaching the spindle cell and the large round-cell type.

At the upper inner surface of the tumor on the right side, the cells under the capsule can be recognized as atypical cells of the zona glomerulosa. Their cordons are very irregular, being composed of flattened indistinctly outlined cells with deep staining irregular nuclei; they are continuous with large thick solid bundles of oval cells, the outer layer alone being recognized as cells from the glomerular zone.

In the moon-shaped cap described in the gross, lying on the lower border of the right adrenal tumor, there are masses of medullary or chromaffin cells, sharply angular with a large amount of eosin-staining cytoplasm. They are somewhat larger and more irregular than the normal medullary cells, and in mass are separated sharply from the surrounding tumor tissue.

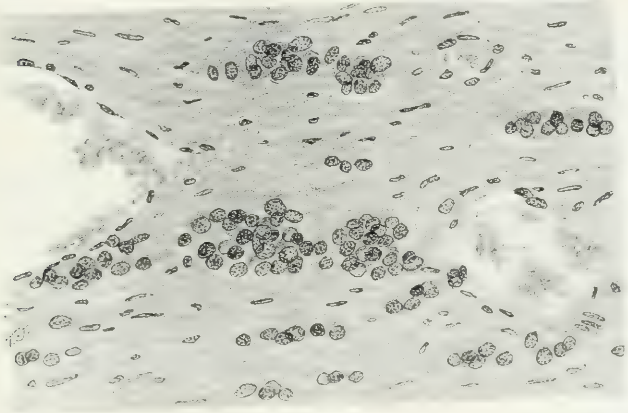

Fig. 4.—Dog A. Capsule of adrenal tumor infiltrated by strings and small masses of tumor-cells. The cells are polygonal, with a small amount of dense purplish-staining cytoplasm, and an irregular deep-staining nucleus.

The capsule of both the right and the left tumor is infiltrated by strings and small masses of tumor-cells arranged quite like the strings of carcinoma cells at the edge of a carcinoma simplex (Fig. 4). These cells are medium-sized polygonal cells, with a purplish-staining dense cytoplasm and an irregular deep-staining nucleus. For the most part, these chains of cells do not penetrate except into the inner two-thirds of the capsule. In several places, however, they have broken through the capsule (Fig. 5) and are found in irregular masses in the loose connective tissues on the outside. Small bunches of them are found in large spaces, apparently lymph-spaces in the connective tissue and areolar tissue outside the tumor. Their appearance outside of the capsule is a little different from that within the interstices of the capsule, in that, outside, both the nucleus and the cytoplasmic outline of the cells are irregularly flattened. The capsule is entirely broken through in places by masses of these cells. In several sections are found irregular giant-cells of the myeloid type, either singly or in small groups. In no place throughout either tumor are there any tubule formations like those described in about half the cases of renal hypernephromas. Histologically, both tumors are essentially solid.

There are veins on the surface of the right adrenal capsule that have been thrombosed, the lumen now being in the process of canalization. A careful search for adrenal metastases was made in other parts of the body, but none were found.

As a summary of the anatomical findings in Dog A, there are: (1) adenocarcinoma of the thyroid with metastases in the lungs, mediastinum and pineal region; (2) bilateral primary adrenal mesothelioma, the local picture being that of early though definite malignancy; (3) bilateral congenital multicystic kidneys; and (4) cavernous hemangioma of the liver.

Case 2.—Dog B is a large, old female. The neck is diffusely enlarged, while in the posterior mammary region there is a nodular, rather soft mass from 4 to 6 cm. in thickness, 8 cm. wide and about 13 cm. in length.

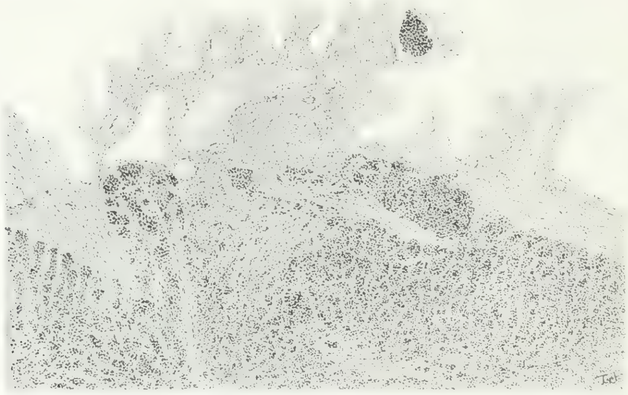

Fig. 5.—Dog A. Capsule of adrenal tumor under low power. In several places the tumor-cells have broken entirely through the capsule and are found in irregular masses in the loose connective tissue outside, and also in large spaces, apparently lymph-spaces.

Thyroid: The thyroid gland is quite like that of Dog A with the exception that it is not quite so fibrous and not so large. There are a few lymph-nodes in the cervical region of both sides that contain white metastatic tumor-nodules. The tumor is very vascular, the vessels containing numerous papilliferous tumor thrombi.

Lungs: The lungs alone contain thyroid metastases, of which there are about fifty, ranging in size from 1 mm. to 1 cm. in diameter. They are spherical and of a whitish-gray color.

Mammary Tumor: The right posterior mamma is more involved than the left, though both are involved by the tumor. The skin is immovable over the mass but is not ulcerated. The tumor is roughly nodular, the nodules being from 2 to 5 cm. in diameter, and indistinctly separated from one another by a softer internodular tissue. On the surface made by sectioning the tumor it is seen that the border of the tumor is indefinite in its separation from the surrounding normal tissue; in places it has a very delicate capsule. The region between the nodules is milky white, and soft or gelatinous in consistency. These nodules are nothing more than irregular firm cartilaginous centers surrounded by softer tissue. The transition between the soft and the firmer tissues is a very gradual one.

Adrenals: The adrenals are twice as large as normal. They are firm in consistency.

The remaining tissues reveal no pathological changes that are of importance in this case.

Microscopic: The tumor of the thyroid is of the adenocarcinomatous variety, tending toward the solidum or simplex type; in this respect it differs from the carcinoma of the thyroid in Dog A. The alveoli here are incompletely formed in most instances, and contain a granular eosin-staining substance, more like albumin than like colloid.

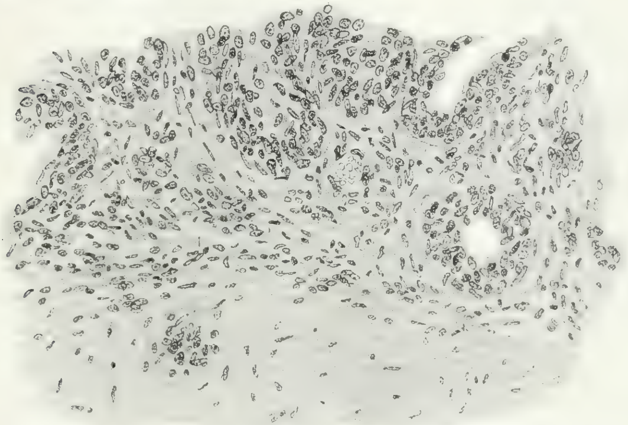

Fig. 6.—Dog B. Mammary tumor. The softer portions of this tumor are composed of a wildly proliferating sarcomatous-like connective tissue, in which there are various-sized tubule formations: some are solid while others have empty lumina, and are lined with cells from three to six layers deep; these cells do not resemble endothelial or epithelial cells, but are of an intermediate type. The above-mentioned type of tissue runs into a myxomatous tissue, and this in turn into an embryonal cartilaginous tissue.

The metastases in the cervical lymph-nodes are similar to the original thyroid carcinoma tissue. The nodules in the lungs are all metastases from the thyroid tumor. They are located in the blood-vessels; the smaller ones consist of irregular cell-nests tending to alveolar formation, in places, set in a hyaline-like tissue; the larger nodules have a distinct fibrous stroma in which there are blood-vessels. The cells, though, in places tending to form alveoli are for the most part arranged in no particular manner.

Mammary Tumor: The edges of this tumor are faintly limited by a delicate connective-tissue capsule which is, in places, lacking. The outermost tumor-tissue, which is a diffusely proliferating sarcomatous-like connective tissue, corresponds to the soft gelatinous internodular tissue described in the gross. The latter has in many places no limiting connective-tissue capsule between it and the normal tissue. The soft tissue is composed of irregular-sized spindle-cells, the fibrillae of which approach that of embryonal connective tissue in character. The spindle-cells are arranged in no regular fashion, but are confused and run in all directions (Fig 6). Within the tissue mentioned above lie many various-sized, twisted and compressed tubule formations, the lumina of which are distorted and empty. The cells lining these tubules are arranged in irregular stratified formation, from four to six cells deep. They do not resemble endothelial cells or epithelial cells, but are of an intermediate type.

In the centers of the tumor nodules there is invariably found a cartilaginous tissue which is not mature or typical in any place. At its edges it fades into a myxomatous tissue, into a mucoid substance, or into the above-described sarcomatous-like connective tissue. This microscopic picture is quite identical with that of the mixed tumors of the parotid gland described by Wilson and Willis.[28]

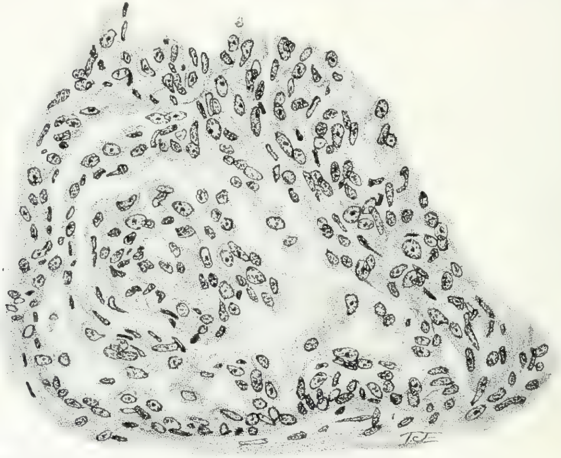

Fig. 7.—Dog B. Mammary tumor. A high-power drawing of an incompletely formed tubule, with its surrounding sarcomatous-like connective tissue.

There are no detectable metastases from this tumor, yet the histological character of the sarcomatous connective tissue on the advancing border of the tumor indicates probable malignancy. The older portions in the centers of the nodules are composed of a tissue approaching the adult type. The peripheral portions can be considered as a more embryonal and undifferentiated mesodermal tissue.

Adrenals: These, though grossly normal except for slight enlargement, are very interesting histologically, in that from fifteen to twenty-one small intracapsular adenomas, composed of cells similar to the zona glomerulosa, are found in any one cross-section.

Briefly, then, in Dog B there are the following: (1) adenocarcinoma of the thyroid gland with metastases in the lung; (2) mixed tumor of the mammary gland (chondrosarco-endothelioma); and (3) multiple adenomas of the adrenal capsule.

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[28] Wilson, L. B., and Willis, B. C.: Mixed Tumors of the Salivary Glands, Am. Jour. Med. Sc., 1912, cxliii, 656.

COMMENT

What inference may we draw from these two cases? Is there any one etiological factor responsible for the development of these multiple primary malignant tumors in either case, or are they incidentally multiple?

It is well known that malignant disease of the thyroid gland in man and in the dog is more prevalent in goitrous districts than in non-goitrous districts. In Great Britain, where goiter is not prevalent, only seven cases of malignant disease of the thyroid were found in 7,294 necropsies.[29] In Vienna, where goiter is not uncommon, Hinterstoisser[30] found fifty malignant tumors of the thyroid in 18,147 necropsies. On the other hand, in Berne, where goiter is common, Limacher[31] found eighty-two cases of malignant disease of the thyroid in only 7,641 necropsies; thirty-eight of these were carcinoma, while forty-four were sarcomas. Marine and Lenhart[32] have shown from their work on brook-trout that the goiters of fish are entirely due to metabolic disturbances from food and external conditions. They[33] state the following in reference to malignant disease of the thyroid gland: "Goiter in some way favors the development of cancer, just as it favors the development of benign tumors. Cancer developing in an otherwise normal gland is extremely rare. We have never observed thyroid cancer apart from preexisting goiter."

The ordinary goiter in dogs is due usually to a diffuse enlargement of the gland, and rarely to adenomas; Marine and Lenhart assert that fetal and that simple adenomas are never found in dogs. In and about Chicago, where goiters in dogs are very common, carcinoma of this gland is not at all infrequently found.

In both Dogs A and B there is nothing that indicates a preexisting developmental anomaly; presumably the thyroid carcinomas in both cases were preceded by, and indirectly due to, a diffuse hyperplasia, which in turn is no doubt, so far as is known, a manifestation of metabolic disturbance dependent on the water and food.

In Dog A, in addition to the thyroid carcinoma, there are the bilateral adrenal hypernephromas, or better, "mesotheliomas," so far as it has been rather conclusively shown that renal hypernephromas and adrenal hypernephromas are distinct from each other both embryologically and histologically. These two adrenal tumors have undoubtedly originated from an anomalous embryonal development, since they are bilateral, and are associated with bilateral, congenital, multicystic kidneys. The cavernous hemangioma of the liver is of doubtful embryonal development. There is, then, nothing in common in the etiology of the thyroid carcinoma and of the double adrenal mesothelioma, one being of probable indirect metabolic origin, while the others are from embryonal anlages. Their location does not suggest that they are the result of any one tissue susceptibility, the adrenals being of mesothelial origin, while the thyroid is of ectodermal origin.

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[29] Müller, G. P., and Speese, J.: Malignant Disease of the Thyroid, Univ. Penn. Med. Bull., 1906, xix, 74.

[30] Hinterstoisser, H.: Beiträge zur Lehre vom Schildrüsenkrebs, Beitr. z. Chir. Festschrift-Billroth, 1892, p. 287.

[31] Limacher: Quoted by Müller and Speese. (See Footnote 29.)

[32] Marine, D., and Lenhart, C. H.: Observations and Experiments on the So-Called Thyroid Carcinoma of Brook-Trout and Its Relation to Ordinary Goiter, Jour. Exper. Med., 1910, xii, 311.

[33] Marine, D., and Lenhart, C. H.: Pathological Anatomy of the Human Thyroid Gland, The Archives Int. Med., 1911, vii, 506.

In Dog B, besides the carcinoma of the thyroid gland, there is the mixed tumor of the mammary gland, similar in structure to those mixed tumors in the parotid gland. This tumor, like the adrenal tumors in Dog A, without much doubt is of embryonal origin. It is closely allied to the teratomas, having cartilage, myxomatous tissue, endothelial structures and a sarcomatous stroma. The various grades of teratoma and mixed tumors are most frequently found in the ovaries, testes, parotid gland and mammary gland. In Dog B the occurrence of multiple capsular adenomas of the adrenals is significant of an imperfect embryonal development.

Both the malignant tumors in Dog B, then, also are, as in Dog A, very probably of different etiology, the one being due indirectly to metabolic disturbance, and the other, the mixed tumor, being in some way connected with an embryonal anlage. One is of ectodermal and the other of mesodermal origin.

SUMMARY

Multiple primary malignant tumors occur in approximately 0.2 per cent. of all cases of malignant tumors.

Certain of them that originate close together in one type of tissue are indicative of a localized tendency to malignant degeneration.

Others that are essentially bilateral, occurring in the ovaries, testicles, kidneys and adrenals, are indicative of a tissue predisposition, dependent in most instances on an anomalous embryonal development.

Besides these two classes there is another general class of cases, two-thirds of which is composed of multiple primary malignant tumors, the location and arrangement of which is strongly indicative of a system involvement, affecting mainly the reproductive, the gastro-intestinal and the cutaneous systems.

In the other third of this class of cases, the tumors are distributed miscellaneously, and apparently have no common features. The two cases here reported belong to the latter class, each animal having one tumor dependent indirectly on a metabolic disturbance, and another tumor distinctly of embryonal anlage.

I wish to thank Dr. D. J. Davis for his kind suggestions in the compilation of this paper.

1532 Congress Street.

FATTY INFILTRATION (LIPOMATOSIS) OF THE AURICULOVENTRICULAR BUNDLE OF HIS, WITH SUDDEN UNEXPECTED DEATH *

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Numerous studies have established a definite relationship between the symptoms usually referred to as Adams-Stokes disease and changes in the auriculoventricular bundle of the heart, the bundle of His. The absence of sufficient information in many of the reports in a recent summary by Bachman[1] led him to base this definite relationship on the evidence in only twenty-four of the eighty-six cases reviewed; in the remainder the details were inadequate for comparison.

In these twenty-four, to which I have added a few[2] not in the number considered by Bachman, the alterations found in the His bundle were as follows:

Condition	Cases
Gumma	7
Fibrosis	7
Calcified plaques	3
Lipomatosis	2
Round celled infiltration	3
Arteriosclerosis of the bundle vessels	2
Tumor	1
Anemic infarct	1
Parenchymatous degeneration	1

From a study of such a table as this it is evident that well-marked examples of the Adams-Stokes syndrome have for their explanation a lesion of the auriculoventricular bundle. A number of careful studies have shown that a complete transverse lesion of the main stem of this conducting system is followed by a total heart-block.

It is possible, however, that when the auriculoventricular bundle possesses alterations only a portion of the symptoms regarded as essential for the Adams-Stokes syndrome are manifested. Beginning or partial involvement of the bundle may lead simply to a lengthening of the inter-

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* Submitted for publication Dec. 5, 1913.

* From the Pathological Laboratory of the Rush Medical College.

[1] Bachman: A Physiologico-Pathological Study of a Case of Heart-Block Occurring in a Dog as a Result of Natural Causes, Jour. Exper. Med., 1912, xvi, 3.

[2] Keith and Miller: Lancet, London, 1906, ii, 1429; Heinecke: Drei Fälle von Adams-Stokes Krankheit, Berl. klin. Wchnschr., 1907, xliv, 1125; Karscher and Schaffner: Ein Fall von Adams-Stokes 'scher Krankheit mit Schwiele im His 'schen Bündle, Berl. Klin. Wchnschr., 1908, xlv, 1266.

systolic period.[3] Or there may be only bradycardia, tachycardia, arhythmia or cyanosis.[4] Furthermore, in a few instances sudden death has occurred without, so far as known, any illness with symptoms leading to even a suspicion of Adams-Stokes disease. Mönckeberg[5] has reported two such occurrences.

The first was diphtheria with sudden death. Mönckeberg does not state at what period in the disease death occurred. No gross changes were found in the myocardium at the post-mortem examination. The auriculoventricular bundle and its many branches when sectioned serially in paraffin and stained by Van Gieson and hematoxylin appeared normal. Using Scharlach R., however, the main stem, both branches and their subdivisions were found to be the site of a distinct fatty change which sharply differentiated this system from the fat-free myocardium.

In Mönckeberg's second example sudden death followed trephining of the skull, as a result of caries of the frontal bone. The myocardium presented fatty changes. In Scharlach R. preparations both divisions of the His bundle stood out in marked contrast due to the greater fatty change that was present in them. Yet there were individual fibers among these unaffected and normal in all respects.

Acute fatty changes similar to these and caused by septicemia, pneumonia, typhoid fever, diffuse bronchitis and chloroform poisoning have been studied by Sapegno.[6] Among other results of the studies of seventy-two hearts he concluded that rapid, unexpected death of an individual, in whom no other anatomic alteration is found, may be due to an acute or a chronic lesion of these peculiar fibers in the heart. He also believes that while fatty changes are often present in both the myocardium and the bundle system together, yet in 50 per cent. of all instances these acute changes affect especially the conducting system.

Similar alterations have also been found by Aschoff[7] in the His bundle. He has not, however, observed any instance in which such a change was responsible for the sudden death.

Marked fatty changes of an *entirely different* sort than those discussed by Mönckeberg, Aschoff and by Sapengo as quoted above, may be very extensive in the His bundle, as is well shown by the following report of fatty infiltration or replacement of the His bundle by adipose tissue associated with sudden death.

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[3] Erlanger: On the Physiology of Heart-Block in Mammals with Especial Reference to Causation of Adams-Stokes Disease, Jour. Exper. Med., 1906, viii, 8.

[4] Von Neusser: Disorders of the Respiration and Circulatiton, 1908 (New York), Part 2, p. 18.

[5] Mönckeberg: Untersuchungen über das auriculo-ventricular Bundle bei Mann, Jena, 1906, Cases 71 and 104, p. 318.

[6] Sapegno: Nuove Ricerche sulla Patologia del Fascia atrioventricolare, Arch. per le Sc. med., 1910, xxxiv, 549.

[7] Referat über die Herzstörungen in ihrem Beziehungen zu den Spezifischen Muskelsystem des Herzens, Verhandl. d. Deutschen. patholog. Gesellsch., 1910, xiv, 3.

History.—A man 38 years of age, who had always been well, died suddenly. Friends stated that at times he had seizures during which he trembled generally and voluntarily or consciously shook his hands and forearms rapidly. These only lasted a moment or two and there was no loss of consciousness. So far as is known he never sought medical advice.

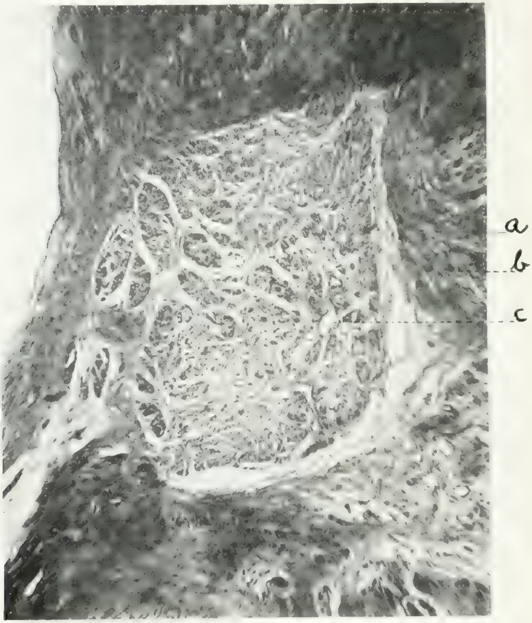

Fig. 1.—A transverse section through the distal portion of the normal node of the His bundle at a point in its passage through the auriculo-ventricular fibrous ring. a. Bundle fibers. b. Fibrous connective tissue surrounding the bundle. c. Bundle vessels.

Necropsy.—The body was that of a powerful, well-nourished white man with no external injuries. There was no excess of subcutaneous adipose tissue. The organs were found to be of normal size and position. There were no gross evidences of disease anywhere. Careful examination of the gastro-intestinal tract failed to disclose any alterations leading to a suspicion that death might have resulted from poisoning, nor did the circumstances attending his death indicate this possibility.

The heart was not hypertrophied and in so far as could be ascertained by gross examination was normal in all respects save for a slight degree of coronary sclerosis and a moderate fibrous myocarditis. There was no abnormal deposit of fat on the outside of the heart.

"There are approximately two small nodules in each coronary artery. The first nodule in each vessel is 1.5 cm. distal to the sinus of Valsalva. The nodules involve the intima of the vessel wall chiefly and the lumen is but slightly lessened in each instance. On tracing the coronary arteries to their terminal endings no occlusions are found. The vessels are not tortuous and the walls are elastic."

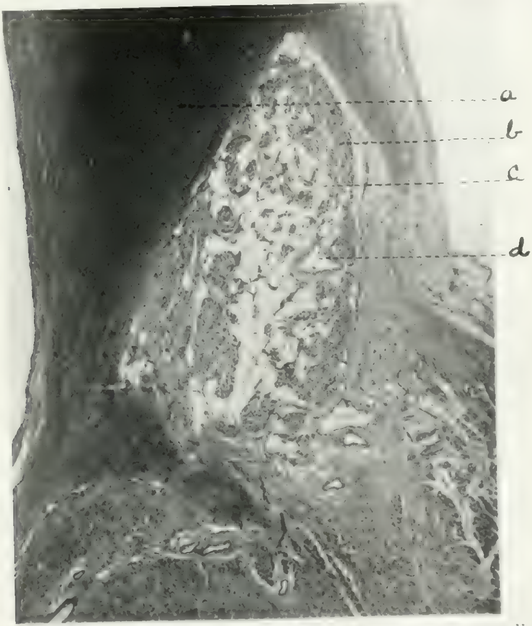

Fig. 2.—Adipose tissue in the node. a. Central fibrous body surrounding the node. b. Intact bundle fibers. c. Adipose tissue. d. Bundle vessels.

Portions of both the right and left ventricular walls, the septum and papillary muscles were examined at various levels to determine the amount of fibrosis.

"The septum contains only a normal amount of fibrous connective tissue. The fibrous tissue in the ventricular walls is somewhat increased in amount. At all points this increase is only slight and but few true muscle fibers are replaced. This change is not especially prominent in any portion of either ventricular wall. The amount of fibrosis in the papillary muscles is even less than that observed in the outer ventricular wall."[8]

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[8] Dr. E. R. LeCount, who conducted the post-mortem examination, was of the opinion that the gross changes in the heart were inadequate to explain death.

The following anatomic diagnosis was made:

"Slight nodular sclerosis of the coronary arteries; slight fibrous myocarditis; slight fibrous mural endocarditis; passive hyperemia of the liver, spleen, kidneys, pancreas and small bowel; petechial hemorrhages in the large and small bowel and in the pleura of the right lung; marked chylangiectasis of the vessels of the small bowel—post-mortem (?); hyperplasia of the tracheo-bronchial lymph-nodes, of the mesenteric lymph glands, of the spleen, of the solitary follicles of the small bowel and of the lymphoid tissue of the pharynx; marked emphysema of both lungs; edema of the pharyngeal mucous membrane; caseous infratracheal lymph-nodes; fibrous patch in the pia of the left frontal lobe of the brain; slight sclerosis of the aorta and of the vessels at the base of the brain; fibrous adhesions between the gall-bladder and the first portion of the duodenum; fibrous pleuritis; small fibrous patches in the anterior mitral leaflet; slight fibrous subepicardial and supra-arterial nodular pericarditis; marked right halux valgus; carious and missing teeth."

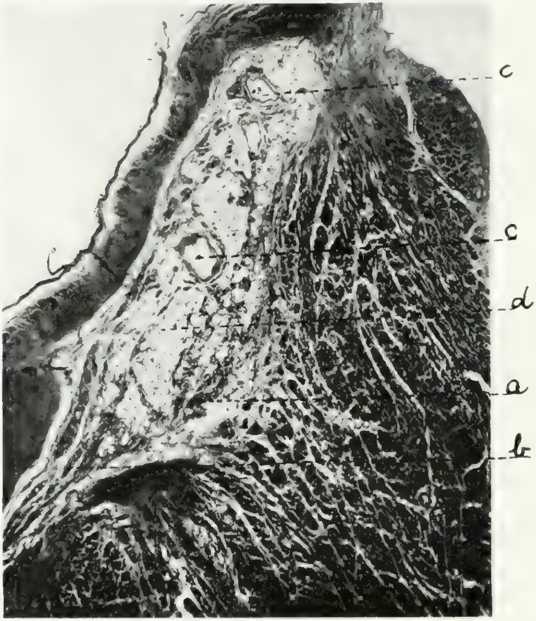

Fig. 3.—Section distal to that shown in Fig. 2. Two-thirds to three-fourths of the bundle fibers are replaced by adipose tissue in this and adjacent sections. a. Intact bundle fibers. b. Beginning of left ramus. c. Bundle vessels. d. Adipose tissue.

Because the gross alterations were so few a study of the His bundle was undertaken. Histological examination was carried out by means of serial paraffin sections of the entire bundle down to and for a considerable distance beyond the point of origin of the right and left branches. Further study was made of the terminal extensions at various levels in the ventricular walls. Every fifth section was mounted and various stains employed.

In these sections there is a very marked fatty infiltration limited strictly to the auriculoventricular bundle and its branches, the myocardium containing no adipose tissue. This change is moderate in the nodal region, more marked in the main stem. At the point of origin of the right and left branches nearly the entire bundle is absent and in its place there is adipose tissue. Both of these branches and the Purkinje fibers at whatever plane examined present such alterations in varying degree.

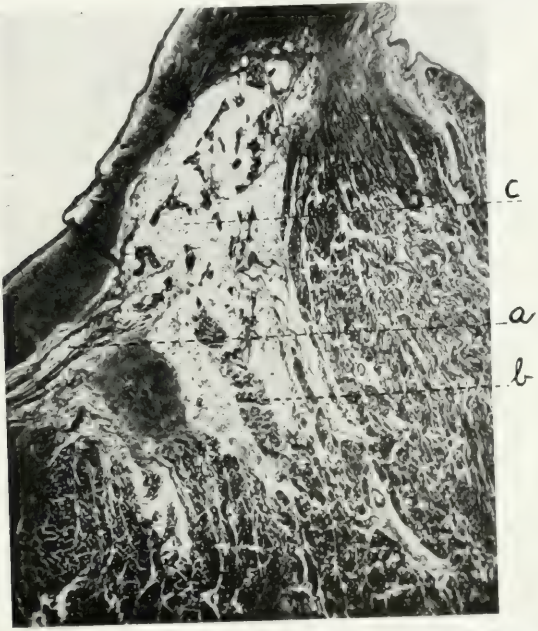

Fig. 4. Section distal to that shown in Fig. 3. A portion of the left ramus and the beginning of the right ramus are present here. In this section 85 to 95 per cent. of the bundle fibers are replaced by adipose tissue. a. Left branch of bundle. b. Beginning of right ramus. c. Main portion of bundle.

Both the muscle fibers and the connective tissue of the bundle system are replaced by adipose tissue. If that part of the bundle lying between the proximal part of the node and the point of division of the main stem into right and left branches is arbitrarily divided into three segments then approximately 20 per cent. (Fig. 2) of the fibers and connective tissue framework of the first segment of the bundle is replaced by adipose tissue, 65 to 75 per cent. (Fig. 3) of the middle segment and 85 to 90 per cent. (Fig. 4). of the distal segment is similarly affected. Just distal to the bifurcation of the bundle 50 per cent. of the structure of the right branch is replaced by adipose tissue while at a similar location in the left branch only 10 to 15 per cent. of the fibers are so affected. These alterations are present, as before stated, in the terminal portions of this specific system of muscle fibers throughout their subendocardial course. The adipose tissue, limited sharply to the Purkinje fibers, differentiates this system at a glance from the surrounding myocardium. In fact their location is readily determined with a hand lens or the low power of a microscope and followed from section to section by the adipose tissue-fat holes at such points.

Some of the muscle cells of the Purkinje fibers are normal. Others on cross section show fat globules in their centers. These globules vary in size from small droplets to larger drops which replace a portion of the protoplasm, leaving the fibrillae standing out very sharply about the periphery of the cell (Fig. 5a). Again, the fibrillae may divide the cell into small fields, the center of these fields being occupied by fat droplets (Fig. 5b). Or the muscle cell may be so distended with fat globules that the remaining fibrillae have all been crowded into one corner of the cell, many of them absent. Finally the entire muscle fiber with its fibrillae, cell membrane and surrounding sheath of connective tissue may be entirely absent and its place taken by adipose tissue.

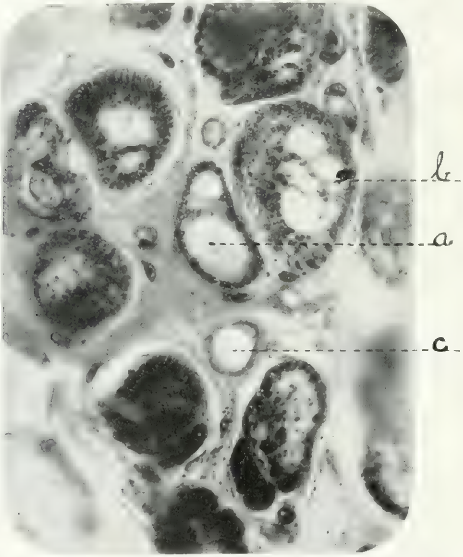

Fig. 5.—Terminal "specific" muscle fibers sectioned across, phosphotungstic acid hematoxylin stain. a. Typical arrangement of fibrillae about the cell periphery. Protoplasm in center of cell replaced by fat. b. Fibrillae dividing cell into fields. Center of fields occupied by fat. c. Entire cell almost entirely replaced by adipose tissue.

As a rule, this replacement by adipose tissue, lipomatosis, which is quite regularly found in the auriculoventricular bundle system of elderly people is not extensive enough to lead to clinical manifestations, yet Fahr[9] has reported so marked a lipomatosis of the bundle that the Adams-Stokes complex resulted and finally death. Aschoff and Tawara[10] have made a similar observation, but Sapegno[11] states in his second article that they later denied the occurrence of a true Adams-Stokes symptom-complex in this instance.

Sapegno[11] describes a lipomatosis found in the His bundle in the heart of a young girl who died twelve days after recovery from typhoid fever. He is very positive in his statements that death in this instance, which was sudden, was not due to the acute fatty changes in the myocardium which are sometimes observed after typhoid fever. Furthermore, this young girl had a cardiac insufficiency which was present from birth and the lipomatosis of the bundle which he found he regarded as congenital. On account of the absence of other gross alterations or processes of disease in the body, death was attributed to the presence of the very marked lipomatosis of "from the point of division of the main branch into two rami to a point where these again decrease rapidly in size."[12]

He concurs with Mönckeberg in recognizing that there is a tendency toward adiposity of the auriculoventricular system in old age, and that while, as a rule, this adiposity is accompanied by fatty infiltration of the myocardium generally, that the bundle alone may be affected and possess grossly visible fat.

In conclusion, without attempting to predicate that death in this instance was necessarily due to these alterations in the His bundle, it is believed that such an examination as this in instances of sudden death with symptoms of cardiac disease, where there are relatively few gross changes in the heart, should be more frequently made. As has been suggested by other investigators of conditions in the auriculoventricular bundle, the nerves connected with it should also be examined.

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[9] Fahr: Cited by Mönckeberg: Berl. klin. Wchnschr., 1909, xlvi, Part 2, p. 45.

[10] Aschoff and Tawara: Die Pathologische-anatomische Grundlagen der Herzschwache, Fisher, Jena, 1906.

[11] Sapegno: Ricerche sulla patologia del fascia atrio-ventricolare, Arch. per le sc. med., 1910, xxxiv, 143.

[12] The original is as follows: "Il cusicinetto adiposo si mantiene sempre di una massa notecole fino alla divisione del f. nei suoi due rami, al qual livello diminuisce rapidamente di volume e cessa quasi del tutto."

BLOOD-PRESSURES

THEIR RELATION TO EACH OTHER AND TO PHYSICAL EFFICIENCY *

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In this communication we desire to record the blood-pressure findings in a total of 742 males with particular reference to the diastolic and pulse pressures; also the relations between blood-pressure and physical efficiency.

METHODS

In these blood-pressure readings we used a mercury manometer of the usual type with 12 cm. cuff, and we made our determinations by the auscultatory method.

The maximum pressure was determined in all cases at the first sound. The minimum pressure in Series A was read at the time of disappearance of all sounds (fifth phase); and in Series B, more accurately at the point of the last clear sound preceding the final dull tones. This is known as the fourth phase. Obviously, then, we get a reading somewhat higher when we make our readings at the final sharp tone than if we wait for the disappearance of all sounds. The difference may be as much as 10 mm. and usually in the neighborhood of 5 mm. This difference, while noteworthy, is not sufficiently great to detract from the actual value of our figures for the minimum blood-pressure in Series A in the manner in which we use them.

The subjects in this study were students in their usual health, most of them between 15 and 25 years of age. While our records include the readings in both the erect and horizontal posture, the accompanying tables and figures refer only to the readings in the erect, the effect of change of posture on the arterial and venous pressures having been previously studied by us.[1]

The method used in estimating the physical efficiency in this work is the one known as the "intercollegiate standard." It consists of adding the strength of back, plus strength of legs, plus strength of right and left forearms, plus lung capacity divided by twenty, plus body-weight divided

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* Submitted for publication Jan. 6, 1914.

* From the Department of Student Health, Carnegie Institute of Technology.

[1] Barach, J. H., and Marks, W. L.: Effect of Change of Posture without Active Muscular Exertion on the Arterial and Venous Pressures, Archives Int. Med., 1913, xi, 485.

by ten. The last figure obtained is multiplied by the number of times the subject pulls up and dips his body by the strength of his arms and shoulder muscles. This gives us a very fair estimate of the individual's physical condition. For one to show a high total strength he must possess a good musculature, good coordination, an efficient circulatory and respiratory system, one which will respond properly and maintain itself during the effort required by the test.

MINIMUM PRESSURES

In the accompanying tables it will be noted that we do not give the average height of the blood-pressure readings of an entire series of cases, but rather do we give the actual number of cases which occurred at the various heights. We believe this to be more accurate and leading to truer conclusions.

TABLE 1.—Age Distribution in a Series of 552 Consecutive Cases

Age, Years	Cases
15 to 17	27
17 to 19	200
19 to 21	202
21 to 23	71
23 to 25	31
25 to 27	12
27 to 29	6
29 to 31	1
Over 31	2
Total	552

Maximum Pressure.—As heretofore stated, the maximum pressure was read at the first sound—by the auscultatory method. In 656 cases the distribution was as shown in Table 2.

TABLE 2.—Distribution of Maximum Pressure in 656 Cases

Mm. Hg.	Cases
90-100	7
100-110	23
110-120	112
120-130	204
130-140	153
140-150	95
150-160	45
160-170	14
170-180 180-190 190-200	3
Total	656

Out of these 656 cases, there are 594 under 150 mm. Hg.: these comprise 90 per cent. of the entire series. It has been our experience that just about 10 per cent. of the men come in presenting a blood-pressure considerably higher than normal at their first examination, but at a subsequent examination it is found to be much nearer the normal level. This undoubtedly is due to the psychic effect of the examination.

Minimum Pressure, Series A.—Here the pressure was read by the auscultatory method at the disappearance of all sounds, with the results shown in Table 3.

TABLE 3.—Minimum Pressure Read by the Auscultatory Method at Disappearance of Sounds

Mm. Hg.	Cases	
30- 40	1	
40- 50	2	
50- 60	4	
60- 70	20	327 Cases = 96 %
70- 80	82	
80- 90	140	
90-100	78	
100-110	9	
110-120	1	
120-130	1	
Total	338	

The majority of these, 96 per cent., had a minimum pressure under 100 mm. Hg.

Minimum Pressure, Series B.—In these cases the point of the minimum pressure was read at the last clear sound preceding the final dull tones (Table 4). It is now generally agreed that this is the exact point of the minimum pressure.

TABLE 4.—Minimum Pressure Read at the Last Clear Sound

Mm. Hg.	Cases	
40- 50	1	
50- 60	4	
60- 70	12	273 cases or 87 %
70- 80	41	
80- 90	94	
90-100	121	
100-110	27	
110-120	9	
120-130	3	
Total	312	

In this series, in which the point of minimum pressure is read earlier than in Series A, we find that over 87 per cent. of the cases present a minimum pressure under 100 mm. Hg, and that 256 cases, or 82 per cent., occur between the points of 70 mm. and 100 mm. Hg.

We see, then, that when the minimum pressure is read at the fourth phase, 87 per cent. of the cases are found to be not over 100 mm. Hg, while at the end of the fifth phase 96 per cent. of the cases do not exceed 100 mm. Hg.

In Series B, in which the pressure was read at the fourth phase, the 13 per cent. which had a maximum pressure of over 100 mm. were reexamined. We then found that the first was only a temporary response to the psychic effect of the examination and that in only two cases did the minimum blood-pressure exceed 100 mm., one showing a minimum blood-pressure of 105 and the other 102 mm. Hg.

Minimum Pressure in All Cases.—If we allow for clinical purposes that the difference between the end of the fourth and fifth phase in a large series of cases such as this one is a negligible factor, by combining Series A and Series B we get the results shown in Table 5.

TABLE 5.—MINIMUM PRESSURE IN ALL CASES

Mm. Hg.	Cases	
30- 40	1	600 cases or 92 %. Not over 100 mm. Hg
40- 50	3	
50- 60	8	
60- 70	32	
70- 80	123	
80- 90	234	
90-100	199	
100-110	36	
110-120	10	
120-130	4	
130-140	..	
Total	650	

Pulse-Pressures.—In Series A and B we have pulse-pressure readings in 629 cases. The normal variation in the size of the pulse-pressure is seen to be quite marked.

TABLE 6.—PULSE-PRESSURES IN SERIES A. MINIMUM PRESSURE READ AT THE FIFTH PHASE

Mm. Hg.	Cases
10-20	9
20-30	30
30-40	68
40-50	76
50-60	62
60-70	43
70-80	17
80-90	7
Total	312

TABLE 7.—PULSE-PRESSURE IN SERIES B. MINIMUM PRESSURE READ AT THE FOURTH PHASE

Mm. Hg.	Cases
5- 10	1
10- 20	11
20- 30	45
30- 40	79
40- 50	79
50- 60	53
60- 70	25
70- 80	18
80- 90	5
90-100	1
Total	317

Tables 6, 7 and 8 show clearly that we may hold the usual pulse-pressure as ranging between 20 and 70 mm. Hg. in healthy persons of the ages here referred to.

TABLE 8.—Pulse-Pressure in Series A and B Combined

5- 10	1	
10- 20	20	
20- 30	75	560 cases or 88%. Between 20 and 70 mm. Hg.
30- 40	147	
40- 50	155	
50- 60	115	
60- 70	68	
70- 80	35	
80- 90	12	
90-100	1	
Total	629	

RELATION BETWEEN THE PULSE-PRESSURE AND DIASTOLIC PRESSURE

Strassburger[2] attempted to find a blood-pressure quotient by dividing the pulse-pressure by the maximum pressure, but that has been shown to be erroneous. It has recently been stated by Stone[3] that the pulse-pressure in the normal individual is equal to 50 per cent. of the diastolic pressure, and that for clinical purposes we may assume that, when the pulse-pressure is over 50 per cent. of the diastolic pressure, we are dealing with cardiac overload. If this theory could have been proved, it would have been an important advance in our clinical work.

We set forth here the findings in 742 cases. Series A has its slight error on account of the minimum pressure having been read at the fifth phase, while in Series B this element is eliminated. The figures represent the percentage relation of pulse-pressure to diastolic pressure. Our formula is D.P.:P.P.::100:×.

TABLE 9.—Series A. Minimum Pressure Read at Fifth Phase

Per Cent.	Cases			
10- 20	10			
20- 30	24			264 cases, 70%
30- 40	48		201 cases, 60%	
40- 50	49	108 cases, 30%		
50- 60	59			
60- 70	45			
70- 80	39			
80- 90	23			
90-100	14			
100-110	16			
110-120	2			
120-130	1			
130-140	5			
Total	335			

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[2] Strassburger: Arch. f. klin. med., 1905, lxxxv.

[3] Stone, Willard, J.: The Clinical Significance of High and Low Pulse-Pressures with Special Reference to Cardiac Load and Overload, Jour. Am. Med. Assn., Oct. 4, 1913, p. 1256.

TABLE 10.—SERIES B. MINIMUM PRESSURE READ AT THE FOURTH PHASE

Per Cent.	Cases			
5- 10	2			
10- 20	8			
20- 30	44			333 cases, 81%
30- 40	63		260 cases, 63%	
40- 50	73	141 cases, 34%		
50- 60	68			
60- 70	56			
70- 80	29			
80- 90	32			
90-100	11			
100-110	13			
110-120	1			
120-130	2			
130-170	5			
Total	407			

In Series B, in which the pulse-pressure is smaller than in Series A, we note that a greater number of cases occur in the lower percentages. In both A and B we may note that the greatest number of cases do occur near the 50 per cent. mark, and if we were to strike an average it would be close to 50 per cent.; yet this would be far from representing the actual truth. These tables show that there is a wide range both above and below the 50 per cent. mark in normal individuals. Our findings here would warrant only a statement that the pulse-pressure equals from 20 to 80 per cent. of the diastolic pressure in about 75 per cent. of the cases. One objection may be offered to our deductions, and that is the comparative youth of the subjects. Considering the age, the physical development, the height of the blood-pressures, and in the light of our previous observations on older subjects, we incline to believe this objection a negligible factor, and that our findings here are representative for normal persons up to middle life. Other observations on older individuals in health and in various disease conditions with which we expect to deal in another paper, will bear out this point.

RELATION OF TOTAL STRENGTH TO BLOOD-PRESSURES

We have pointed out previously[4] that there is no constant relation between blood-pressures and total strength. In Table 11 we show that there is no definite relation between the pulse-pressure per centage of diastolic pressure and circulatory efficiency, such as is indicated by the general physical efficiency.

The upper 146 cases give a pulse-pressure equal to 56 per cent. diastolic pressure, while the lower 150 cases (excluding the last three) give a pulse pressure equal to 61 per cent. of diastolic pressure, showing that there is no relation between the total strength and pulse-pressure per cent. of diastolic pressure.

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[4] Barach, Joseph H.: Physiological and Pathological Effect of Severe Exertion (the Marathon Race) on the Circulatory and Renal System, THE ARCHIVES INT. MED., 1910, v, 382.

It is particularly worthy of note that the man who showed the highest total strength (1724), had a pulse-pressure equal to 100 per cent. of the diastolic pressure. This man certainly had no evidence of cardiac overload. Also that one subject whose strength was only 651 (the fourth lowest of the 344 cases), showed a pulse-pressure equal to 80 per cent. of the diastolic pressure.

TABLE 11.—The Relation of Total Strength to Blood-Pressures

Total Strength	Cases	Av. Str.	Average Max. P.	Average Min. P.	Average P. P.	Average P. P. %
400- 500	1	477	117	75	42	56
400- 500	2	445	134	82	50	62
600- 700	1	651	126	70	56	80
600- 700	5	860	129	66	44	54
600- 700	3	647	121	80	41	54
700- 800	5	774	129	88	41	47
800- 900	5	860	129	66	44	54
800- 900	10	865	123	75	47	64
200- 900	35	871	126	84	41	51
900-1,000	3	927	130	83	46	59
900-1,000	19	950	126	81	42	53
1,000-1,100	28	1,045	121	78	42	51
1,000-1,100	4	1,093	117	83	33	45
1,000-1,100	25	1,048	138	67	51	66
1,100-1,200	14	1,161	123	84	39	48
1,100-1,200	34	1,152	130	84	45	54
1,100-1,200	27	1,148	124	75	46	66
1,200-1,300	4	1,243	136	86	49	57
1,200-1,300	22	1,250	135	83	50	66
1,200-1,300	28	1,242	127	80	45	58
1,300-1,400	5	1,331	120	79	40	52
1,300-1,400	9	1,331	135	86	47	55
1,300-1,400	13	1,347	121	76	44	63
1,400-1,500	5	1,456	133	89	44	50
1,400-1,500	12	1,437	137	85	50	60
1,400-1,500	8	1,465	128	76	50	66
1,500-1,600	2	1,566	121	85	36	42
1,500-1,600	8	1,542	133	80	58	73
1,500-1,600	4	1,537	129	84	45	54
1,600-1,700	1	1,633	132	70	62	88
1,600-1,700	1	1,658	115	68	47	69
1,700-1,800	1	1,724	140	70	70	100
Total.......	344					

Comparing the weak and strong halves of the series, which is representative of the subjects who are more likely and those who are least likely to have circulatory inefficiency and cardiac overload, we see that the pulse-pressure percentage of diastolic pressure can offer us no reliable index.

In a former work[4] it was shown that the size of the pulse-pressure is influenced by the systolic pressure, and that the systolic pressure is much more responsive, even to slight influences, than is the diastolic pressure. We must also take into this consideration the fact that the unit of diastolic pressure has a greater value than the unit in systolic pressure.

As time goes on and our observations accumulate and are being interpreted, we believe that more and more importance will be attached to the height of the minimum pressure, and that the height of the maximum pressure will be considered of lesser clinical import than heretofore. Certainly the maximum pressure alone is of no value excepting as a starting-point for a guess as to the activity of the circulatory system.

SUMMARY

1. In 90 per cent. of a series of 656 healthy young men the maximum blood-pressure was under 150 mm. Hg. It would be still lower if we could eliminate psychic effect.

2. In 96 per cent. of a series of 338 cases the minimum pressure when read at the fifth phase did not exceed 100 mm. Hg.

3. In 87 per cent. of a series of 312 cases the minimum pressure, when read at the fourth phase, did not exceed 100 mm. Hg.

4. On reexamination of the 13 per cent. in the series of 312 cases, we found that 99.4 per cent. had a minimum blood-pressure not over 100 mm. Hg.

5. In 92 per cent. of the total 650 cases the minimum pressure did not exceed 100 mm. Hg at the time of the first examination.

6. In 88 per cent. of a series of 629 cases the pulse-pressure ranged between 20 and 70 mm. Hg.

7. There is no constant relation between the pulse-pressure and the diastolic pressure. In 75 per cent. of a series of 712 cases the pulse-pressure comprises anywhere from 20 to 80 per cent. of the diastolic pressure.

8. There is no relation between physical efficiency, which also means circulatory efficiency, and pulse-pressure percentage of diastolic pressure. In a series of 344 cases, the poorer half gave practically the same pulse-pressure to diastolic pressure percentage as the stronger half, with their better circulatory system.

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THE MECHANISM OF CARDIAC DISPLACEMENTS IN PULMONARY TUBERCULOSIS *

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Monographs on tuberculosis which devote considerable space to the physical diagnosis of this disease usually omit a discussion of cardiac displacements which are so frequently encountered in chests affected by infiltration, fibrous degeneration, collapse, shrinkage and cavitation of pulmonary tissue. Some mention is occasionally made of dextrocardia as liable to occur in extensive right-sided lesions, but minor degrees of displacement, which are so frequently taking place, are altogether forgotten. Some clinicians, however, have observed that dislocation of the heart occurs in pulmonary tuberculosis more often than is generally appreciated. Turban[1] said that a displacement of the cardiac dulness several centimeters to the right, with or without displacement of the heart, is such a frequent symptom of moderate contraction of the right apex that he considers it a typical and cardinal symptom of right apical disease of some standing, and that it may be seen in many cases before the appearance of tubercle bacilli in the sputum.

In their work on fibroid diseases of the lung, Sir Andrew Clark, Hadley and Chaplin[2] show that of forty-five cases of pulmonary fibrosis, thirty-four had cardiac displacements from a half to 3 or 4 inches out of its normal place. Similar conditions were found by these authors in cases of fibroid phthisis.

In this country Pottenger[3] has given the subject of cardiac displacement in tuberculosis considerable attention. He found dislocation of the heart in some form and to some degree in all cases where either a lessening or increase in the volume of the lung occurs. In another paper[4] he gives the following statistics as to its frequency: Of 162 hearts examined, 58 were in practically the normal position, 27 were displaced to the right and 77 were displaced to the left. Of the first-stage cases

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* Read before the Section on Medicine of the New York Academy of Medicine, Oct. 21, 1913.

* Submitted for publication Nov. 6, 1913.

[1] Turban, K.: Diagnosis of Tuberculosis of the Lung, London, 1906, p. 81.

[2] Clark, Hadley and Chaplin: Fibroid Diseases of the Lung, London, 1894, pp. 157, 171.

[3] Pottenger, F. M.: Displacements of the Heart and Diaphragm in Pulmonary Tuberculosis, Interstate Med. Jour., 1911, xviii, 605.

[4] Pottenger, F. M.: The Effects of Tuberculosis on the Heart, THE ARCHIVES INT. MED., 1909, iv, 306.

one was displaced and 10 were in normal position; of the second-stage cases, 4 were displaced and 17 were in normal position, and of the third-stage cases, 99 were displaced and 31 were in the normal position.

In a clinical study of 2,344 cases of tuberculosis made at the Phipps Institute,[5] it was found that the heart was displaced in but 57 instances: 12 times downward, 31 times to the left and 14 times to the right; of the last group, 5 were cases of complete dextrocardia. On the other hand, Lawrason Brown[6] finds that while in the incipient stage the heart is rarely appreciably displaced, in many patients in moderately advanced stages the ordinary methods of exploration show some changes in the position of the heart. From roentgenographic studies, C. L. Leonard[7] found in a series of 100 cases of tuberculosis 26 displacements of the heart and aorta; in 17 it was displaced to the right, in 4 to the left,

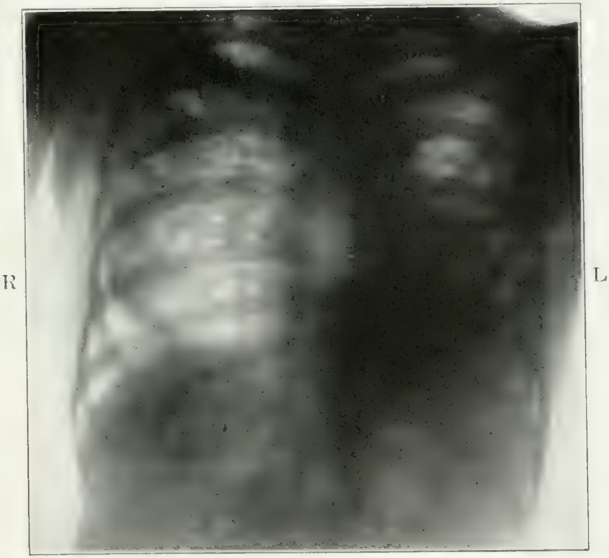

Fig. 1.—Cavity in left upper lobe; thickened pleura at left base; heart displaced to left and downward. Aorta and trachea also dislocated.

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[5] Norris, G. W.: Ann. Rep. Phipps Institute, 1906, ii, 235.

[6] Brown, Lawrason: The Heart in Pulmonary Tuberculosis, Am. Jour. Med. Sc., 1908, cxxxvi, 819.

[7] Leonard, C. L.: Compensation by Displacement of the Thoracic Viscera in Pulmonary Tuberculosis, Med. Rec., 1912, lxxxi, 1.

and in 5 a rotation took place with an upward displacement of the heart and aorta, so that the heart assumed an anteroposterior position. Leonard is of the opinion that marked alterations in the position of the intrathoracic viscera occur in the earlier stages of tuberculosis without visible changing of the excursion of the thoracic wall. Similarly, Francine† found that in many cases of phthisis the heart as well as the aorta, are displaced. He found it in 37 per cent. of cases, and is of the opinion that dislocation to the right is more frequent than to the left. When the pulmonary lesions are of fairly symmetrical character on both sides the heart is more commonly displaced to the right than to the left, according to Francine.

In a recent paper Felix Oeri[8] reports 413 cases of tuberculosis in which the position of the heart was carefully studied. He found that in 43 per cent. of right-sided lesions and 82 per cent. of the left-sided lesions the heart was displaced, or more or less shifted to the affected or more affected side. It appears from Oeri's investigations that dislocations are more likely to occur toward the left side, a view already expressed by Lawrason Brown.[6] This is not because left-sided lesions are more frequent—in fact, they are not—but for anatomical reasons to be discussed later on. Ruedinger,[9] on the other hand, states that dislocations of the heart in phthisis is more frequently directed toward the right side than to the left. Cases of tuberculosis of the right lung in which no cardiac dulness can be discerned to the left of the sternum are not rare. He explains it by the fact that the right lung is the larger lung, and its force of retraction is more powerful, so that traction on the mediastinum will be more effective when pulling it out of its normal location than retraction of the smaller left lung. On the other hand, Lawrason Brown points out that it is readily seen that the displacement of the heart may be much more pronounced when the right lung is affected, for the displacement is most often associated with contraction of one lung. In right apical lesions of some standing, even when the physical signs are slight, the right border of the absolute cardiac dulness may be found ¾ inch or more to the right. Brown states, however, that marked displacement of the heart occurs much more frequently to the left than to the right, owing, possibly, to the fact that the tension, when the left lung contracts, is exerted more directly on the heart. For these reasons a very frequent displacement of the heart is upward and slightly outward. The heart, however, may be so greatly displaced to the left, following contraction of the left lung, or pneumothorax, or pleuritic effusion on the right, that the apex may be beyond the left anterior axillary line or in the third intercostal space.

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† Francine, A. P.: The Effects of Tuberculosis on Intrathoracic Relations, Am. Jour. Med. Sc., 1910, cxxxix, 732; Intrathoracic Displacements in Pulmonary Tuberculosis, Bull. Johns Hopkins Hosp., 1910, xxi, 244.

8. Oeri, Felix: Herzverschiebung bei Lungentuberkulose, Beitr. z. Klin. d. Tuberk., Brauer's, 1913, xxvi, 123.

9. Ruedinger, E.: Die Organverlagerung bei Phthise, Beitr. z. Klin. d. Tuberk., Brauer's, 1910, xvii, 151.

My own experience with tuberculous patients is in agreement with that of Pottenger, Brown and Oeri. In a large number of cases of phthisis in which I looked for the position of the heart while examining the thorax, I found the heart dislocated in such a large proportion that I wonder why text-books do not mention it, and why most clinicians overlook it. In advanced cases of tuberculosis it is exceptional to find the heart in its normal place. It appears, however, that even pathologists have overlooked this fact, or at least have not taken note of it, perhaps because post-mortem conditions do not show vividly the true location of the heart and its relations to the surrounding lungs, especially in minor degrees of displacement. Leonard[7] mentions a pathologist who did not believe that displacements could occur so frequently in the earlier stages of the disease; but since his attention was drawn to it, he found dislo-

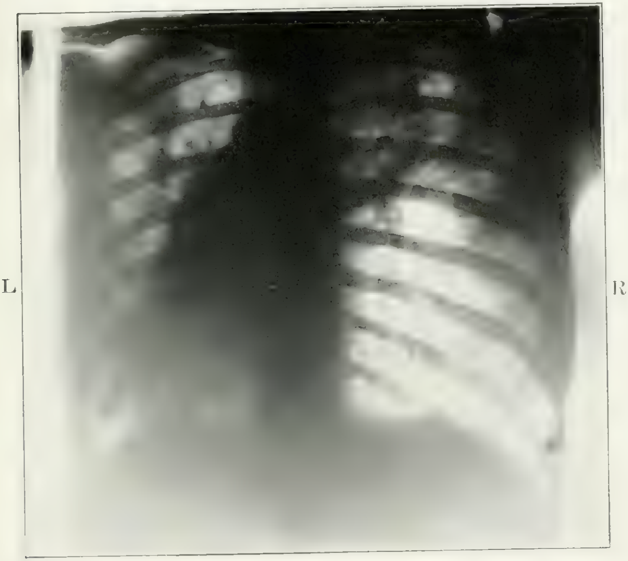

Fig. 2.—Cardiac displacement to the left and upward: bilateral pulmonary lesion with cavity in left upper lobe. Note dislocation of the aorta to the left.

cations very frequently at necropsies. It is only since roentgenography has become a routine method of examination in these cases that the displacements of the heart in tuberculosis are being appreciated. It seems to me that by determining the location of the heart, we can, as a rule, determine in which side the tuberculous lesion is located, or in bilateral lesions which side is the older or more serious lesion, that is, accompanied by destruction of lung-tissue and shrinkage.

Of 115 consecutive cases of pulmonary tuberculosis in which within the last three months I have taken notes on the location of the heart, I found that in 58, or 50 per cent., the heart was dislocated. Of 85 instances with early lesions 31, or 36 per cent., showed cardiac displacements. Of these 22 were displacements to the left and 9 to the right. In other words, 70 per cent. of the displacements were toward the left in early and second-stage cases of tuberculosis. Of 29 far-advanced cases, 27 showed cardiac dislocation, of which 15 were to the left and 12 to the right. Here, again, we have 55 per cent. of displacements to the left.

In the tuberculosis ward of Montefiore Home I found that among 18 far-advanced cases with right-sided lesions, or in which the lesion was more extensive in the right side, 14 showed dislocations to the right and 4 to the left, and in one the heart was in its normal location. Of 19 left-sided lesions, or lesions more extensive on that side, there were 15 displacements to the left, one to the right; in one instance there was no displacement at all. Here the displacements were about equal between the two sides, and, with some exceptions, the shifting of the heart was toward the more affected side. In the cases which did not follow this rule, we always found a reason for the anomaly to be explained later on.

The mechanism of these dislocations of the heart is an interesting topic for study. Experience with intrathoracic tumors, aneurysms, pleural effusions and pneumothorax teaches that the heart is usually displaced toward the healthy side in these cases. While during the course of pulmonary tuberculosis we often encounter cardiac displacements of this kind, as in pleurisy, pneumothorax, etc., yet I do not intend to speak about them in this paper. What concerns us here are displacements in which the heart is displaced toward the affected side, *par attraction,* some French writers call it. In the course of pulmonary tuberculosis, especially in cases running a chronic course, the elastic lung-tissue in the affected region is replaced by fibrous tissue. The lung thus loses its elasticity to a great extent, and its motility suffers greatly. Shrinkage is another feature, thus making room for any intrathoracic organ that may adjoin the affected part. In cases in which there is also vicarious emphysema of the opposite healthy lung—and they are not at all rare—the mediastinum is pushed toward the affected side. Thus in many cases of pulmonary tuberculosis we have in the chest a *vis a tergo* and a *vis a fronte* both effective in displacing the heart toward the affected side.

Within the pericardium the heart is free and smoothly movable; otherwise it could not pulsate regularly and rhythmically. The pericardium is connected above with the deep cervical fascia by a prolongation of the fibrous portion through the sheaths over the great vessels. Two bands of fibrous tissue—known as the sternopericardial ligaments—connect the front of the pericardium above and below with the posterior surface of the sternum. Below, the pericardium is connected with the central tendon of the diaphragm closely and intimately. It is also firmly bound to the caval openings, but loosely attached to and easily separable elsewhere. If its oblique position from right to left, as well as its strong attachment to the diaphragm are borne in mind, it is clear that it requires great force to move the heart to the right, while to the left

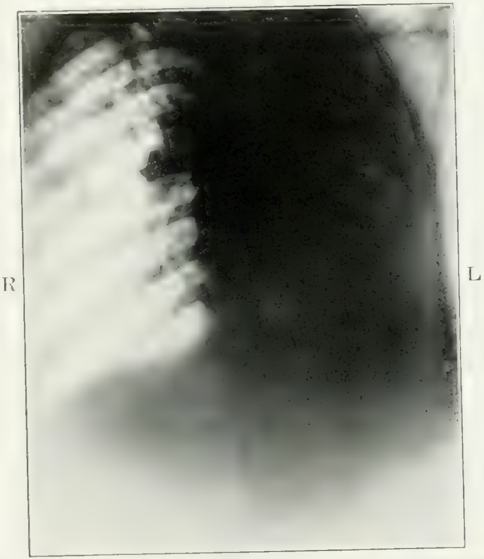

Fig. 3.—Tuberculous pleurisy and cavitation of left lung; heart displaced to the left and downward; apex-beat in left axillary line.

it is more easily shifted. When either traction from the left side or pushing from the right side occurs, and especially when both forces are operative, the only resistance to be overcome is the upper attachment to the great vessels which is yielding, as is evident from the frequent dislocation of the aorta, trachea and even the larynx in cases of phthisis. But when the forces involved are effective in displacing the heart to the right, its intimate attachment to the diaphragm has also to be overcome. It is for this reason that dislocations to the right are more often seen in far-advanced cases of phthisis, especially such as are complicated by, or which follow, adhesive pleurisy; while dislocations to the left may take place in the early stages of the disease.

That the base, in spite of its attachment to the great vessels, is more movable than the apex of the heart, has been proved experimentally and also by roentgenographic studies of cases of pleural effusion by Bard,[10] Pitres,[11] Sallé[12] and many others. It has been found that when fluid is injected into the left pleura there is no displacement of the heart till at least 1,000 c.c. are injected, and only then the heart moves a little to the right, but no more than 2 or 3 cm. When the injection of fluid is continued, the apex hardly moves, held as it is firmly by the central tendon of the diaphragm, but the base does shift to the right, and the whole body of the heart is moved forward, nearer to the anterior chest wall. In cases of left-sided pleurisy with effusion, Carrière[13] has found confirmatory evidence through roentgenographic studies. An effusion of from 700 to 1,000 c.c. does not at all displace the heart; the apex remains in its normal place, and only when the patient assumes an erect posture, or reclines on his right side, does the apex move from 2 to 4 cm. to the right, nearing the median line. In effusions of from 1 to 3 liters the long axis of the heart becomes vertical, the apex is lowered and shifted to the median line; and with an effusion of 3 liters it is moved as far as the xyphoid appendix. When the effusion exceeds this quantity, the heart is shifted completely to the right, but it is not swung over, retaining as it does the normal direction of its long axis from right to left and from above downward—the apex remains at the xyphoid appendix and the base is shifted to the right hemithorax. Torsion is never observed.

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[10] Bard: Refoulement du coeur à droite et dextrocardie congénitale, Lyon méd., 1892, lxxi, 583; 1893, lxxii, 1; Refoulement du coeur à droite dans les épanchements pleuraux, Méd. moderne, 1897, viii, 185.

[11] Pitres: Les signes physiques des épanchements pleuraux et en particulier sur les deplacements du coeur, Arch. clin. de Bordeaux, 1896, v, 1, 65, 241.

[12] Sallé De déplacements du coeur par les épanchements pleuraux gauches au point de vue experimental et clinique, Thèse de Paris, 1908-1909.

[13] Carrière: Dèplacement du coeur et des organs abdominaux dans les épanchements pleuritiques, Presse méd., 1898, vi, 349.

Of course, it is often different with cases of phthisis with strong fibrous bands and pleuropericardial adhesions which immobilize either the apex or the base and keep it in that position. In case the base is immobilized, the apex may move through traction by some other fibrous bands, and the heart assumes a vertical position within the chest, or the axis may be reversed, running from left to right; but this is exceedingly rare. According to the amount, density, location and direction of the adhesions and pulmonary retraction that may be present in a given case of phthisis, the heart may be dislocated upward or downward, to the right or to the left. The apex may be lifted up to an extent as to bring the heart in a horizontal position resting on the elevated diaphragm. Clinical experience shows many of these anomalous dislocations when we look for them.

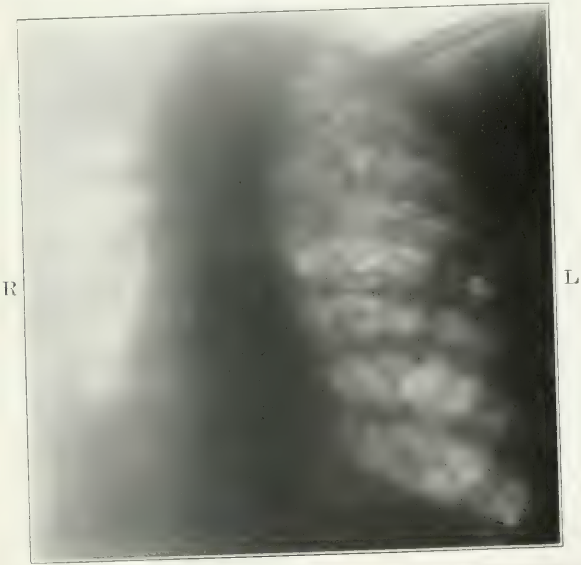

Fig. 4.—Cardiac dislocation to the right with rotation on its sagittal and vertical axes; bilateral pulmonary lesion; adhesive pleurisy in right hemithorax.

The usual location of tuberculous lesions is at the apices, and retraction and scar formation occurs more often in the upper part of the lungs and pleura, thus pulling the heart upward by fibrous bands running to its base from the affected lung or pleura. When the traction comes from the left upper lobe the heart easily yields and moves upward and to the left; when traction is exerted from the right apex, the effect depends on the extent and kind of lesion in the lung. In cases with strong fibrous bands running from the right pleura to the pericardium, especially when there is also cavitation in the right lung making place for its reception—here also Nature abhors a vacuum—and the left lung is emphysematous, encroaching with its bulk on the right side of the thorax, pushing the mediastinum toward the right, all obstacles are overcome more or less and the heart moves to the right side; in extreme cases we may find under these circumstances complete dextrocardia with the apex-beat to the right of the sternum. Shrinkage of the lung takes place in both a horizontal and a vertical direction, and thus not only the mediastinum, but also the diaphragm is often dislocated. Strictly speaking, elevation of the diaphragm in one side will push the heart upward and to the opposite healthy side; but inasmuch as fibrosis and retraction of the lung not only pulls up the diaphragm vertically, but retracts the lung horizontally, the heart is usually attracted toward the affected side. When there is a pulmonary cavity and emphysematous lung on the opposite healthy side, it is evident that the dislocation will be toward the affected side.

In tuberculosis the position of the heart is consequently greatly influenced by the position of the diaphragm. An elevation of the right half of that muscle tends to shift the heart to the left; elevation of the left half of the diaphragm first raises the apex of the heart, bringing it into a horizontal position, and when the height of the left half of the diaphragm greatly exceeds that of the right half, there may occur a dislocation of the heart to the right. When pleuropericardial adhesions are strong and dense they may pull the heart to the left and upward, as we see in many cases of phthisis, especially those following adhesive pleurisy of the left side.

Older writers spoke of a form of cardiac dislocation in which that organ, fixed at its base by the great vessels, was swung over to the right side like a door on its hinges. This has been found erroneous, as has been shown in the excellent anatomical, clinical and experimental studies of Bard,[10] Pitres,[11] Sallé[12] and others; but we do know that rotation on its sagittal and vertical axes often does take place. In the normal position of the heart the left ventricle is nearer the chest wall than the right, which is turned to the back. As Oeri[8] points out, traction exerted on the right side brings the right ventricle nearer the chest wall, while the apex is moved away from it; traction on the left side may increase the obliquity of its position and pull the heart completely toward the left. Cavitation in the left upper lobe, combined with fibrous bands running between the pleura and pericardium, dislocates the heart not only to the left but also upward, and this is greatly assisted by the upward displacement of the diaphragm, as was already mentioned. It must also be borne in mind that the left half of the diaphragm is easily movable.[14] Traction toward the right, if not very strong, may turn the heart on its sagittal, and at times on its vertical axis, and as a result we find an increase in the dulness to the right of the sternum, because the base of the heart has approached the chest wall without much shifting, while the apex, moved as it is backward, cannot be found on inspection and percussion. This explains some of the cases of vertical hearts which we find so often in roentgenograms when examining advanced cases of tuberculosis.

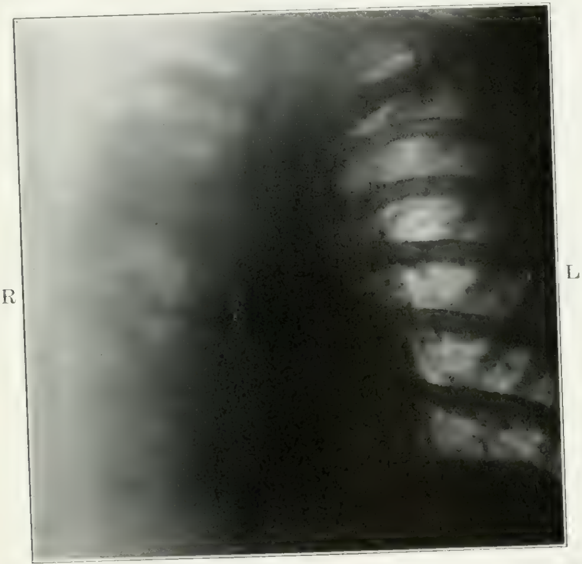

Fig. 5.—Shifting of heart to the right with rotation on its sagittal axis in an extensive right-sided tuberculous lesion.

When we have two forces combined, as in traction on the right side due to dry pleurisy with massive adhesions, pulmonary fibrosis, long-standing tuberculous pleurisy with formation of false membrane, pleuropericardial adhesions which immobilize the heart and fix it in an abnormal position, and an emphysematous lung in the left hemithorax making place for itself by encroaching across the sternum to the right, we may find complete and permanent dextrocardia. In these cases there is no rotation of the heart with swinging all the way around on its point of fixation at the great vessels, as was formerly thought. This would be incompatible with life. As has been shown by recent experimental investigations at the necropsy-table and with the Roentgen ray, the heart is in these cases pushed over to the right hemithorax *in toto*, the base is usually displaced to the same extent as the apex, and it retains its natural oblique position in the chest—its long axis is directed from above downward and from right to left. But instead of lying to the left of the sternum, it is located to the right of the median line of the body. Carefully studied cases of dextrocardia of this type have been reported by Bard,[10] Galliard,[15] Lortat-Jacob and Laignel-Lavastine,[16] Barbier[17] and many others. I encounter these cases comparatively often and at the Montefiore Home I have had four under observation during the last three years. They are very rare in acute cases, running speedily to termination by death, but in those which run a chronic course extending over many years, dextrocardia may occur in extensive right-sided lesions. They also occur in cases of pleurisy which are strongly adhesive from the beginning, and follow rapid absorption of a pleural exudate when the lung does not reexpand quickly to fill up the space left vacant by the disappearance of the fluid. In these cases the pleura forms a thick shell around the collapsed lung into which it sends forth thick fibrous bands. When the latter contract they may drag the mediastinum, thus filling up vacant space in the right hemithorax.

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[14] Sahli: Diagnostic Methods, Second American edition, p. 251.

I want to say a few words about those rare cases of dextrocardia in which the base of the heart remains in nearly its normal position, while the apex is found in the right mammillary line, or even further toward the axilla; the direction of its long axis is from above downward and from left to right. It was this sort of case of dextrocardia that formerly led to the belief that in some dextrocardias the heart is swung over to the right side. As has already been stated, such dextrocardias do not exist because the kinking of the great vessels would promptly extinguish life. These forms of dextrocardia usually occur in the following manner: An effusion into the left pleura pushes the entire mediastinum to the right and keeps it there until the fluid is absorbed or removed. In the vast majority of cases the heart then returns to its normal location

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15. Galliard, M. L.: Dextrocardie par attraction, Bull. et mém. Soc. méd. d. hôp. de Paris, 1908, xxv, 634.

16. Lortat-Jacob and Laignel-Lavastine: Dextrocardie acquise par retraction pleuro-pulmonaire avec caverne tuberculeuse, Bull. et mem. Soc. méd. d. hôp. de Paris, 1906, xxiii, 814.

17. Barbier: Un cas de dextrocardie au cours d'une sclerose pulmonaire tuberculose droite, Bull. et. mém. Soc. d. hôp. de Paris, 1900, xxvii, 187.

on the left side; but in some rare cases in which the right pleura is affected, the apex of the heart, while sojourning in the right hemithorax, is bound down by strong pleuropericardial adhesions, so that while the base, which is free, moves back to its normal place, the apex remains fixed in its abnormal position. Such a case has been reported in detail by Chalier and Rebattu,[18] and in one case that I have seen this was the only plausible explanation for the anomalous position of the heart.

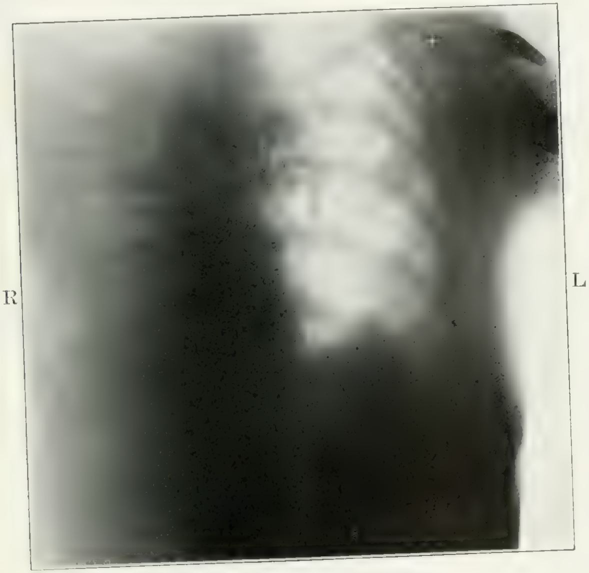

Fig. 6.—Acquired dextrocardia.

While in most cases of cardiac dislocation in tuberculosis the heart is displaced toward the affected side and in bilateral lesions to the side in which the older and more serious lesion is found, there are many exceptions. Pleuropericardial adhesions often prevent dislocation of the heart, which ordinarily would be pulled or pushed out of place. At times we encounter extensive infiltration, or a large cavity in the right upper or middle lobe, while the heart is dislocated 1 or 2 inches to the left. In these anomalous cases I almost invariably found that in addition to the lesion in the right lung, there was also a thickened pleura at the left base, adherent to the left side of the pericardium which pulled and fixed the heart toward the left side.

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[18] Chalier, J., and Rebattu, J.: Des dextrocardies acquises, Paris méd., 1912, p. 365.

The routine methods of physicial exploration show the location of the displaced heart in phthisis easily and vividly; but in many cases the diagnosis is very difficult, and occasionally almost impossible. The side of the heart adjoining the healthy lung is easily made out by percussion, but the cardiac dulness at the side adjoining the affected lung merges with the dulness of the infiltrated and consolidated lung-tissue or thickened pleura, and is difficult to separate by any method of percussion. The fluoroscope and the roentgenographic plate also fail at times to show a definite outline of the borders between the heart and lung. Indeed, I have found in many cases that the orthodiascope was of no value, because extensive infiltration and thickened pleura have obscured all outlines which in normal subjects show such a clear picture of the heart and lungs. The diagnosis of dextrocardia is also sometimes difficult. Of course, from complete transposition of the viscera it is easily distinguished when the location of the liver, spleen, etc., is noted; but when we find the heart on the right side, the apex beating to the right of the sternum and the liver, spleen, etc., in their normal locations, the question may arise whether we are not dealing with one of those rare cases of congenital transposition of the heart in which this is the only organ displaced. This is especially true of cases in which the heart was dislocated by a latent pleurisy during infancy of which the patient can give no account. The electrocardiograph may give us positive information in these cases, as by a study of the records from the different leads the axis of the heart may readily be determined. We had a case at the Montefiore Home in which the question arose whether it was congenital or acquired, and the Roentgen ray could give no positive diagnostic clues. The electrocardiogram taken by Dr. B. S. Oppenheimer, however, showed a normal tracing.

While percussing and auscultating these chests, it is to be borne in mind that the heart is not only shifted from left to right, but in many cases there is also some rotation of that organ on its vertical or sagittal axis—the base approaching the chest wall, while the apex is shifted away from it. As a result it often happens that the point at which the impulse of the apex is apparently found is altogether the impulse of the right ventricle. Occasionally we find two points with impulse beneath—one in the second or third right intercostal space, and another near the xyphoid cartilage. As a general rule, we may say that when on inspection palpation and auscultation we find the heart-beat at only one point, it is the base or the right ventricle which is visible and palpable, because in these cases the apex is turned away from the anterior chest wall; when two points are found with impulses, the one to the left represents the apex and the one to the right represents the base for reasons just made clear.

Even in moderate dislocations we find that the cardiac sounds undergo important modifications. While it is undoubtedly true that the great frequency of the accentuation of the second pulmonic sound, as well as the impulse at the second left intercostal space near the sternum, are due to pulmonary retraction, yet in a large number of cases the dislocation of the heart and rotation on its vertical axis are responsible for it in a great measure. Similarly, often no apex-beat can be seen or felt, although percussion and auscultation show that it is located in its normal place. In some this is due to an emphysematous lung covering the apex, but in others rotation with shifting backward is responsible. At times we find that although the apex is shifted to the left, the cardiac impulse remains within the mammillary line, which is also due to rotation of the heart on its vertical or sagittal axis. The fact is that two cases of cardiac dislocation showing the same signs and symptoms are very rare, which is clear when we bear in mind the various directions

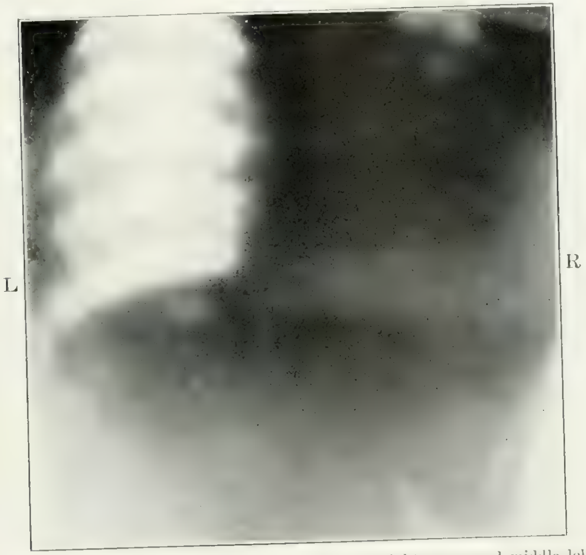

Fig. 7.—Acquired dextrocardia; large cavity in right upper and middle lobes; thickened right pleura; vicarious emphysema of left lung.

in which traction by fibrous bands may be exerted and the different locations of shrinking pulmonary tissue, cavitation, compensatory emphysema, as well as the condition of the pleura in its relation to the pericardium, and above all the position of the diaphragm. It has been my impression that in displacements to the left, the second pulmonic sound is very frequently accentuated, while dislocations to the right are more often accompanied by an accentuation of the aortic sounds. In both cases it may be due to either greater conductivity of densely infiltrated lung tissue, to obstruction of the pulmonary circulation as in emphysema, or to the fact that the base of the heart has been moved nearer to the anterior chest wall.

The effects of cardiac dislocations on the circulation and on the general condition of the patient depend on several factors, especially the rapidity with which it is accomplished, the distance it is dislocated out of its normal position, and also the mode of displacement. Most dislocations are found in very old and chronic cases, mainly in fibroid phthisis, and the effects on the circulation come on slowly and insidiously, the heart adapting itself more or less to its new position. Pottenger[3] observed a case in which the heart moved more than 1 inch to the right within a few days' time owing to the formation of a large cavity in the right lung near the heart border. The symptoms were extreme weakness, dyspnea, rapid heart-action and a tendency to syncope, loss of appetite and nausea, especially when the patient changed his position. In a case under my care, the heart was dislocated upward and to the left about 1½ inches out of place within two weeks, and the patient, a boy aged 15, suffered from extreme prostration, dyspnea and tachycardia, and also showed signs of cerebral anemia.

In all the chronic cases of tuberculosis in which the heart is appreciably dislocated, tachycardia is a constant symptom; but tachycardia is a cardinal symptom of phthisis without cardiac displacement, and has been attributed by various authors to pressure on the vagus by swollen bronchial glands, or fibrous scars, etc., and also to the toxemia of the disease. In cardiac dislocation, however, we have an added mechanical factor. In my experience annoying tachycardia is extremely rare in afebrile cases of phthisis, unless there is also cardiac dislocation, when it becomes an important symptom, and the least exertion results in severe palpitation, dyspnea, weakness, etc. Ruedinger believes that there are undoubtedly forms of tuberculosis in which the rapid heart-action is primarily due to disturbances in the mechanism of the heart as a result of the dislocation. When we examine these cases fluoroscopically, we find obvious reasons for cardiac embarrassment in the displacement of the thoracic organs. Some healed cases of tuberculosis remain permanently with tachycardia, and inasmuch as toxemia cannot be held responsible for the rapid heart-action in inactive cases, the dislocation of the heart may be held accountable.

SUMMARY AND CONCLUSIONS

Cardiac dislocations are very frequently found in pulmonary tuberculosis. In far-advanced cases of phthisis it is exceptional to find the heart in its normal location, over 75 per cent. of cases showing displacements of the heart. In moderately advanced cases between one-third and one-half show displacements, and even some early cases are thus affected.

The dislocation is usually produced by traction exerted from the affected side. Pulmonary collapse and retraction, cavitation and fibrous bands running from the pleura to the pericardium drag the heart out of its normal place. Pressure exerted by a vicariously emphysematous lung on the opposite side greatly assists in displacing the heart to the affected side, or, in bilateral lesions, to the side which has the older or more serious lesion. In many cases we can determine in which side the tuberculous lesion is located, or in bilateral lesions in which side the older or more extensive lesion is located, by determining the location of the heart.

Dislocations take place more often toward the left hemithorax than toward the right for various anatomical reasons, mainly, however, because of the oblique position of the heart from right to left, and the strong attachment of the mediastinum to the central tendon of the diaphragm, which greatly counteracts traction exerted from the right pleura and lung. As a result we find that about two-thirds of all displacements are toward the left side. In far-advanced cases the displacements are about equal between the two sides of the chest, and dextrocardia is not uncommon. Acquired dextrocardia is almost invariably of tuberculous origin.

In many cases of phthisis the heart is not only dislocated, but also rotated on its sagittal or vertical axis. In the normal position the cardiac apex is nearer the chest wall than the base. Traction exerted on the right side of the mediastinum may bring the base of the heart nearer the chest wall and push or pull the apex away from it. Elevation of the diaphragm also has a great influence on the position of the heart, and together with pleuropericardial adhesions may dislocate the heart in any manner—upward, downward, to the right or left; may bring it in a horizontal or vertical position, etc.

In the majority of cases the diagnosis of displacement can be made by percussion, auscultation and roentgenoscopy; but in some cases only the side of the heart adjoining the healthy lung can be mapped out by percussion, while on the opposite side its dulness merges with that of the pulmonary or pleural lesion and cannot be differentiated easily, and at times even the Roentgen ray is of no avail. In dextrocardia a good guide is the cardiac impulse. When we find only one point with an impulse, it is usually the right ventricle that pulsates and not the apex, because in these cases the latter is turned away from the anterior chest wall; if we find two points with pulsation, the one to the left represents the apex and the one to the right the base or the right ventricle.

While tachycardia and dyspnea of phthisis are usually due to toxemia of the disease, the cardiac displacements are also responsible to some extent. Many patients cured of tuberculosis remain with permanent cardiac embarrassment because of the displacement of the heart.

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ANIMAL CALORIMETRY: PAPER VIII. THE ALLEGED INFLUENCE OF THE ADRENALS ON DIABETIC METABOLISM *

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NEW YORK

The discovery by Blum[1] that administration of epinephrin caused glycosuria at once suggested that its action might be due to an effect on the pancreas. This hypothesis was tested by Herter and Wakeman,[2] who found that direct application of epinephrin solutions to the pancreas caused the appearance of sugar in the urine. Benedicenti[3] and Pemberton and Sweet[4] showed that epinephrin injections diminish the flow of pancreatic juice. The last-named authors suggested the possibility that the "internal secretion" of the pancreas was likewise inhibited and therefore diabetes resulted. Edmunds,[5] however, set forth that the inhibition of the pancreatic flow was due to a reduced blood-supply to the gland brought about by vasoconstriction.

An elaborate theory as to the action of epinephrin was promulgated by Falta, Eppinger and Rüdinger,[6] a theory which has had the support of von Noorden,[7] whose pupils these authors were. According to this theory, epinephrin inhibits the internal secretion of the pancreas, thereby preventing the oxidation of sugar; it stimulates the thyroid to increased

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[*] This article and the six following, viz., those of Graham Lusk and J. A. Riche, E. R. Baldwin, J. A. Hartwell, J. P. Houget and Fenwick Beekman, C. F. Craig, Horst Oertel, C. W. Field, and W. W. Herrick are contributions in commemoration of the hundredth anniversary of the foundation of the medical department of Yale University, and will be republished in book form.

[*] Submitted for publication March 3, 1914.

[*] From the Physiological Laboratory, Cornell University Medical College, New York.

1. Blum: Deutsch. Arch. f. klin. Med., 1901, lxxi, 146.

2. Herter and Wakeman: Virchow's Arch. f. path. Anat., 1902, clxix, 479.

3. Benedicenti: Arch. ital. d. biol., 1905, xcv, 1.

4. Pemberton, Ralph, and Sweet, J. E.: The Inhibition of Pancreatic Activity by Extracts of Suprarenal and Pituitary Bodies, The Archives Int. Med., 1908, i, 628.

5. Edmunds: Jour. Pharmacol. and Exper. Therap., 1911, ii, 559.

6. Falta, Eppinger and Rüdinger: Ztschr. f. klin. Med., 1908, lxvi, 1.

7. Von Noorden: New Aspects of Diabetes, 1912.

activity, thereby causing an increase in protein metabolism, and it causes a transformation of sugar into fat.

Although not one of these statements is true, the theory has possessed a charm from which many have not been able to free themselves, and it has also been productive of work which has shown the matter in its proper light.

Thus, Ringer[8] rendered dogs diabetic with phlorhizin according to a method originally perfected at the Yale Medical School by Reilly, Nolan and Lusk,[9] and after freeing the dogs of glycogen by shivering, found that administration of epinephrin caused no increase of either sugar or of nitrogen in the urine. Epinephrin, therefore, does not cause the production of sugar from fat nor does it increase protein destruction through thyroid stimulation.

The present paper deals with the remaining question whether or not epinephrin glycosuria is due to an inhibition of the internal secretion of the pancreas, which thereby renders the organism truly diabetic in the sense that there is a decreased power to oxidize glucose.

This problem has been considered by other authors, but their published results are conflicting. Thus Hári[10] administered epinephrin intraperitoneally and intravenously to curarized dogs from twenty-four to thirty-six hours after the last food ingestion, and found that the respiratory quotient was somewhat increased above the level existing prior to the injection of the drug. The increase in the respiratory quotient was usually coincident with a rise in blood-pressure. Wilenko[11] employed rabbits under urethane anesthesia and found that after the ingestion of sugar the respiratory quotients of normal animals ranged between 0.90 and 0.98. Wilenko found, however, that if epinephrin were administered, the respiratory quotient did not rise under the influence of sugar ingestion. From this he drew the conclusion that epinephrin prevents the oxidation of carbohydrate in the organism.

Fuchs and Roth[12] administered epinephrin subcutaneously to three persons, one of whom had Addison's disease, and found an increase in the respiratory quotient. Similar results which were reported by Falta[13] have been described in full by Bernstein.[14]

The question of the inhibition of carbohydrate metabolism through epinephrin seemed to be in an unsettled state and one which might be determined by experiments with the respiration calorimeter constructed by Dr. H. B. Williams in this laboratory.[15]

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[8] Ringer: Jour. Exper. Med., 1910, xii, 105.

[9] Reilly, Nolan and Lusk: Am. Jour. Physiol., 1898, i, 395.

[10] Hári: Biochem. Ztschr., 1911, xxxviii, 23.

[11] Wilenko: Biochem. Ztschr., 1912, xlii, 49.

[12] Fuchs and Roth: Ztschr. f. exper. Path. u. Therap., 1912, x, 187.

[13] Falta: Die Erkrankungen der Blutdrüsen, 1913, p. 428.

[14] Bernstein: Ztschr. f. exper. Path. u. Therap., 1914, xv, 86.

It may be added that Allen,[16] using other methods, has reached the conclusion that epinephrin glycosuria is without relation to diabetes.

EXPERIMENTAL

The work was accomplished with two dogs. Both animals were given 0.001 mg. of epinephrin (adrenalin hydrochlorid of Parke, Davis and Co.) per kilogram of bodyweight administered subcutaneously. The animals were brought into the calorimeter as soon after the injection as possible. The urine of the period was collected by catheterization. The dogs were very active while under the influence of the drug, exhibiting unrest and polypnea as has been described by various authors. Dog 3, which had rested quietly in the calorimeter on twenty-one previous occasions, became quite violent after receiving epinephrin, incidentally

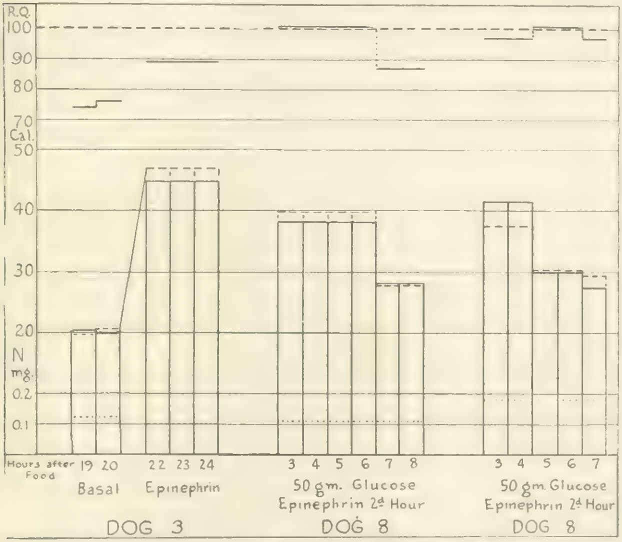

Chart showing the influence of epinephrin on metabolism. Solid lines represent calories calculated, broken lines calories found, and dotted lines milligrams of nitrogen.

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15. Williams: Jour. Biol. Chem.. 1912, xii, 317.

16. Allen: Glycosuria and Diabetics, 1913, p. 1063.

removing the thermometer from the rectum and chewing it into pieces. The rectal thermometer was therefore not used in the experiments with Dog 8. On this account the direct and indirect measurements of heat are not so close together as they might be. A wire netting was made to surround the dog bed so that the valuable internal adjustments of the calorimeter should not suffer damage.

TABLE 1.—

Date		Time	CO_2 gm.	O_2 gm.	R. Q.	H_2O gm.	Urine N gm.	Non Protein		
								CO_2 gm.	O_2 gm.	R. Q.
/28/13	Dog 3	a. m. p. m. 11:00-12:00	6.39	6.13	0.76	8.12	0.120	5.27	5.12	0.75
	Exp. 21	p. m. p. m. 12:00- 1:00	6.38	5.94	0.78	7.01	0.120	5.26	4.93	0.78
	Exp. 22	p. m. p. m. 2:00- 5:00	48.13	39.18	0.89	65.95	0.315	45.18	36.52	0.90
/30/13	Dog 8	a. m. p. m. 11:00- 3:00	61.16	43.39	1.02	103.25	0.428	57.16	39.77	1.04
	Exp. 1	p. m. p. m. 3:00- 5:00	19.67	16.50	0.87	35.74	0.214	17.67	14.69	0.88
5/ 5/13	Exp. 2	a. m. p. m. 11:00- 1:00	31.75	23.92	0.97	51.97	0.354	28.44	20.93	0.99
		p. m. p. m. 1:00- 3:00	24.30	17.18	1.03	45.07	0.354	20.99	14.19	1.08
		p. m. p. m. 3:00- 4:00	10.58	7.90	0.97	20.05	0.177	8.93	6.40	1.01

Necrosis of the skin always follows subcutaneous injections of epinephrin given in these quantities, but no permanent injury ensues. Dog 3 retains a scar on the back at this writing, nearly a year after the treatment, and has experienced fifty experimental periods in the calorimeter.

The full details of all the experiments are given in Table 1, and are graphically illustrated in the accompanying chart.

A. THE EFFECT OF EPINEPHRIN INJECTIONS ON THE BASAL METABOLISM

The *basal metabolism* in this series of papers has been taken as the average heat production during two or three hours of absolute rest following the eighteenth hour after the ingestion of a maintenance ration. Benedict has lately described this metabolism as being "postabsorptive." Since the basal metabolism or *Grundumsatz* may remain at the same level during months or even years, it seems unnecessary to change its name. It appears to be a desirable expression representing a uniform base line which is immediately affected by changes induced by food ingestion, mechanical work, by variations in external temperature, by drugs or by disease.

ETAILS OF EXPERIMENTS

Calories				Body Temperature			Weight, Mg.	Behavior of Dog	Remarks
Pro- ein	Non Pro- tein	Total Calc.	Total Found	Start	End	Dif.			
3.18	16.99	20.17	19.53	37.68	37.39	—0.29	12.15	Quiet.	Basal metabolism.
3.18	16.48	19.66	20.60	.....	37.58	+0.19	.....	Quiet.	
		39.83	40.13						
8.35	125.90	134.25	140.62	38.00	38.83	+0.83	12.15	Very active.	12 mg. epinephrin, 1:13 p. m.
11.52	141.45	152.97	159.32	.....	.....	......	11.0	Very active.	50 gm. glucose, 9 a. m. 11 mg. epinephrin, 10:15 a. m.
5.76	50.37	56.13	55.56	.....	.....	.....	.....	Active and quiet.	
		209.10	214.88						
9.38	73.76	83.14	74.88	.....	.....	......	11.0	Very active.	50 gm. glucose, 9 a. m. 11 mg. epinephrin, 10:16 a. m.
9.38	50.71	60.09	60.24	.....	.....	......	.....	Active and quiet.	
4.69	22.61	27.30	29.51	.....	.....	......	....	Quiet and movement.	
		170.53	164.63						

The basal metabolism of Dog 3 (weight = 12.1 kg.) was determined between 11 a. m. and 1 p. m., beginning eighteen hours after the ingestion of a standard diet consisting of 100 gm. of biscuit meal, 100 gm. beef heart, 20 gm. lard and 10 gm. of bone ash. This diet contains 688 calories, of which 137 calories (20 per cent.) are in protein, 251 (36 per cent.) in fat and 300 in carbohydrate (44 per cent.) The quantity of carbohydrate in the biscuit meal amounted to 73 gm.[17]

At 1 p. m. the dog was removed from the calorimeter, catheterized, and at 1:13 p. m. received a subcutaneous injection of 12 c.c. 1 : 1,000 epinephrin solution. The animal was returned to the calorimeter and the experimental work was resumed at 2 p. m. The animal was extremely active throughout the experimental period of three hours. Between 2

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[17] Lusk: Jour. Biol. Chem., 1912, xiii, 186.

p. m. and 3:52 p. m. (when the rectal thermometer ceased recording) the body temperature of the dog increased 0.83°.

Table 2 shows the influence of epinephrin injection on the basal metabolism of the dog.

This experiment shows that the injection of epinephrin does not increase the nitrogen in the urine. During the period of the basal metabolism, calculations[18] made in the light of the respiratory quotients show that 0.8 gm. of glucose was oxidized per hour, amounting to 16 per cent. of the total heat evolved, while, during the period of epinephrin influence, 7.4 gm. of glucose were oxidized per hour during three hours, yielding 62 per cent. of the total heat produced. The oxidation of sugar was increased ninefold. The results are to be explained by the well-authenticated fact that the administration of epinephrin causes hyperglycemia[19] through discharge of sugar from the glycogen stores of the body.[20] The 22 gm. of glucose oxidized during the three-hour period corresponded to less than 0.2 per cent. of glycogen in the well-nourished dog, a very moderate quantity. The urine of the experimental period was free from sugar, but after the usual standard diet had been administered to the dog following its removal from the calorimeter, the urine became charged with sugar.

The increase of 125 per cent. in the metabolism may be entirely attributed to muscular movements.

This experiment shows that *epinephrin administered twenty-one hours after food ingestion does not prevent the oxidation of glucose in a well-nourished dog.*

B. THE EFFECT OF EPINEPHRIN INJECTIONS ON THE METABOLISM AFTER GLUCOSE INGESTION

Two experiments were performed on Dog 8, a small, fat animal, weighing 11 kg. The standard diet was given daily at 5 o'clock beginning on the evening of April 29. As the dog was not trained to lie quietly in the calorimeter the basal metabolism was not determined. It could scarcely have exceeded 20 calories per hour.

At 9 a. m. 50 gm. of glucose in 150 c.c. of water were given to the dog, and at 10:15 a. m. 11 c.c. epinephrin, 1:1,000, were given subcutaneously; the experiment began at 11 a. m. The results may be condensed as in Table 3.

Experiment 1 shows that the urinary nitrogen was 0.107 gm. per hour, which is not above the usual output of nitrogen during the period

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[18] For the method of calculation see Williams, Riche and Lusk: Jour. Biol. Chem., 1912, xii, 356.

[19] Vosburg and Richards: Am. Jour. Physiol., 1903, ix, 35.

[20] Drummond and Noel Paton: Jour. Physiol., 1904, xxxi, 92.

TABLE 2.—EXPERIMENTS 21 AND 22 ON DOG 3, SHOWING THE INFLUENCE OF EPINEPHRIN ON THE BASAL METABOLISM

	Time	N. in Urine gm.	R. Q.	Calories				
				Protein	Fat	Carbohydrate	Total Calc.	Total Found
Basal metabolism ...	11 a. m. to 12 m.	0.120	0.76	3.18	14.56	2.42	20.17	19.53
Basal metabolism	12 m. to 1 p. m.	0.120	0.78	3.18	12.36	4.12	19.66	20.60
							39.83	40.13
Average per hour.....	....	*0.120*	....	*3.18*	*13.46*	*3.27*	*19.92*	*20.07*
Epinephrin metabolism	2 to 5 p. m.	0.315	0.89	8.35	42.81	83.09	134.25	140.62
Average per hour.....	....	*0.105*	....	*2.78*	*14.27*	*27.70*	*44.75*	*46.87*

TABLE 3.—EXPERIMENTS 1 AND 2 ON DOG 8, SHOWING THE INFLUENCE OF EPINEPHRIN DURING A PERIOD OF GLUCOSE ABSORPTION

Time	N. in Urine gm.	R. Q.	Calories				
			Protein	Fat	Carbohydrate	Total Calculated	Total Found
11 a. m. to 3 p. m...	0.428	1.02	11.52	20.55	141.45	152.97	159.32
3 to 5 p. m......	0.214	0.87	5.76		29.82	56.13	55.56
						209.10	214.88
11 a. m. to 1 p. m...	0.354	0.97	9.38	2.76	71.00	83.14	74.88
1 to 3 p. m......	0.354	1.03	9.38		50.71	60.09	60.24
3 to 4 p. m......	0.177	0.97	4.69		22.61	27.30	29.51
						170.53	164.63

of basal metabolism of a dog nourished on the standard diet employed in this laboratory. In Experiment 2 the nitrogen elimination was found to be 0.177 gm. per hour, an abnormally high figure, undoubtedly due to the necrosis of the skin brought about by the previous injection of epinephrin.

In Experiment 1 there was an elimination of 7.9 gm. of glucose in the urine during seven hours following the injection of epinephrin. Deducting this amount from 50 gm. actually ingested, there remain 42.1 gm. available for oxidation. The respiratory quotient of the six hours of the experiment was 0.98. Calculating as before, it appears that 46 gm. of glucose, or 7.7 gm. per hour, were actually oxidized to furnish 171.27 calories liberated from carbohydrate in the organism. This represents 82 per cent. of the total heat production during the period. Since the metabolism experiment did not commence until two hours after the administration of the glucose, it is evident that the carbohydrate oxidized during the six hours of the experimental period counted some glycogen drawn from the body's store of that material.

It may be argued that epinephrin injection might produce an effect on the pancreas which might render it more susceptible if the injection were given a second time. The experiment was, therefore, repeated in all its essentials on the same dog five days later. The dog had received the standard diet at 5 p. m. daily during the interim.

In Experiment 2 there was an elimination during six hours of 11.1 gm. of urinary glucose, leaving available for metabolism 38.9 gm. of 50 gm. ingested. During the experimental period of five hours, the respiratory quotient averaged 0.99. The heat produced from carbohydrate was 144.32 calories, which is the equivalent of 38 gm. of glucose, representing an hourly destruction of 7.6 gm. In this instance, 85 per cent. of the total calories of metabolism were derived from glucose.

Comparing these results with former work[21] accomplished on a normal dog which had received 50 gm. of glucose, it becomes evident that *the injection of epinephrin in the dog has no influence on the metabolism of carbohydrate during the period of glucose absorption.*

The cause of epinephrin glycosuria is best explained by the work of Ritzmann,[22] who found that sugar appeared in the urine only when the dose of the drug was sufficient to cause vasoconstriction. Such a condition may bring about anemia of the tissues, under which circumstance there is always a production of lactic acid, a discharge of glucose from the glycogen repositories, a marked increase in the quantity of blood-sugar and consequent glycosuria. Lactic acid may stimulate the respiratory center, causing polypnea. The oxygen absorption is such, however, that anemia of the tissues can only be relative, and is not such as to prevent a large oxidative energy production.

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[21] Lusk: Jour. Biol. Chem., 1912, xiii, 27.

[22] Ritzmann: Arch. f. exper. Path. u. Pharmakol., 1909, lxi, 231.

SUMMARY

The subcutaneous injection of epinephrin in a well-nourished dog twenty hours after the ingestion of a standard mixed diet sufficient for maintenance caused an increase of the respiratory quotient from 0.77 to 0.89. From the former quotient it may be calculated that 16 per cent. of the heat production was at the expense of glucose, while from the latter it appears that 62 per cent. had that source. Before the injection of epinephrin, 0.8 gm. glucose was oxidized per hour, and after the injection 7.4 gm. per hour. The dog became muscularly active about half an hour after the administration of the drug.

The subcutaneous injection of epinephrin in a dog which had received 50 gm. of glucose resulted, in one experiment, in a respiratory quotient for a six-hour period of 0.98, and a combustion of glucose amounting to 7.7 gm. per hour, corresponding to 82 per cent. of the heat production of the period. On repetition of the experiment six days later, the respiratory quotient was found to be 0.99 during a period of five hours, and the oxidation of glucose amounted to 7.6 gm. hourly, being the equivalent of 85 per cent. of the total calories produced.

The heat produced from the oxidation of 7.5 gm. of glucose is 28 calories, and the basal metabolisms of the dogs did not exceed 20 calories per hour. This is suggestive that epinephrin does not cause a diminution in the power of the organism to oxidize glucose.

The theory that epinephrin causes a production of sugar from fat, decreases the power of the organism to oxidize glucose through inhibition of pancreatic function, and stimulates the thyroid so that protein metabolism is increased, is untenable in any of its particulars.

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EXPERIMENTAL STUDIES ON THE BLOOD-SERUM OF COWS IMMUNIZED AGAINST TUBERCULOSIS

*"SENSITIZATION" OF LIVING TUBERCLE BACILLI**

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The experiments given in detail in this contribution relate to some calves that were immunized in 1902 and 1903 by intravenous inoculations of human tubercle bacilli. The results of various serum reactions, including complement deviation, agglutination and precipitation, were published in 1904.[1] Bactericidal and bacteriolytic tests, which were briefly described at that time,[2] were also performed with culture bacilli.

Nearly all the calves were killed at the conclusion of the first-mentioned experiments. Calf 5 was, however, retained for more than ten years, being repeatedly inoculated with cultures and extracts of tubercle bacilli. These were always of the human type, so that the actual test of immunity-inoculation of bovine bacilli was never made. Nevertheless, from the well-known protection acquired by calves under similar treatment, it is fair to assume that this animal was at least relatively immune.

The further study of immune serums in general, and of this animal especially, appeared of sufficient importance to indicate its retention, as in the course of time additional knowledge of serology was developed.

So far as can be discovered from a search of the literature, no instance is mentioned of an immunized bovine being observed over so long a period. At least, no observations of the blood-serum have extended over such a long time, to the best of our knowledge. It seemed, therefore, a sufficient reason for publishing some of the experiments, although they are chiefly of interest to laboratory workers in tuberculosis.

Some of the experiments have already been reviewed.[3] Of these, many were tests for opsonin or bacteriotropin, but the difficulty of deter-

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* From Saranac Laboratory for the Study of Tuberculosis, Dr. E. L. Trudeau, Director.

* Submitted for publication March 3, 1914.

[1] Studies from the Saranac Laboratory, Jour. Med. Research, 1904, xii, 215.

[2] Studies from the Saranac Laboratory, Jour. Med. Research, 1904, xii, 226.

[3] Opsonins in Tuberculosis, Tr. Assn. Am. Phys., 1907, p. 517.

mining the varying content of these substances by a normal standard serum was not overcome, owing to the agglutination. It was shown that a specific bacteriotropin was present, but it could not be measured.

Previous experiments had failed to produce antitoxic serums for tuberculosis, so that no extensive trial was made of the neutralizing effect of the immune cow-serums. Neither was the trial made of serum injections on animals or man with the hope of restraining infection as in the more recent experiments of Neporoschny,[4] Ruppel and Rickman,[5] Calmette and Guérin,[6] Pawlowsky,[7] and Sata.[8] The harmful effects of foreign serums in producing anaphylaxis have long been recognized as a drawback to serotherapy. Notwithstanding this, Neporoschny, Ruppel and Sata asserted that their serums, when injected into guinea-pigs, retarded infection. Calmette and others found similar serums harmful and the disease aggravated.

Our interest was centered in the plan of "sensitizing" living tubercle bacilli with immune serums. It was hoped that by saturating tubercle bacilli or their products with the immune antibody from serums, a better vaccine or tuberculin might be produced. The serum *per se* could thus be washed out but its specific virtues retained, anchored to the bacilli.

Within the past three years such a vaccine, made from B. E. tuberculin sensitized by Ruppel's serum, has been patented in Germany by F. Meyer[9] and has been employed as a mild-reacting tuberculin under the designation "S. B. E." It is said to have diminished toxicity in comparison with plain B. E. Neporoschny also used such a vaccine for immunizing dogs, whose serum in turn was employed in the treatment of tuberculosis.[10] We could not show any lessening of toxic effects of B. E. by our experiments.

As our work was with living, intact bacilli and with cow-serums of lower antibody content than the horse- and mule-serums used by Ruppel, it is not possible to say that our results are contradictory in this respect, though it would so appear in the methods here described.

In the details which follow, some protocols of our first attempts at bacteriolysis are included for the sake of completeness.

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4. Neporoschny, S. D. (quoted by Pawlowsky): Ztschr. f. Tuberk., 1911, xvii, 8.
5. Ruppel, W. G., and Rickman, W.: Ztschr. f. Immunitätsforsch., 1910, vi, 344.
6. Calmette, A., and Guérin, C.: Ann. de l'Inst. Pasteur, 1911, xxv, 629.
7. Pawlowsky, A. D.: Ztschr. f. Tuberk., 1911, xvii, 1.
8. Sata, A.: Ztschr. f. Tuberk., 1911, xviii, 1; 1913, xx, 1.
9. Meyer, F.: Berl. klin. Wchnschr., 1910, No. 20, p. 926.
10. Neporoschny, reviewed by Piel P.: Beitr. z. Klin. d. Tuberk., xxi, 311.

BOVINE IMMUNIZATION; WEAK-VIRULENT HUMAN BACILLI

Bactericidal Influence of Immunized Serum from Heifers Nos. 4, 5 and 6 on Cultures

The following notes were made in 1903 of the first tests made with the serum of No. 5 together with others (Nos. 4 and 6). The animal was then 11 months of age and weighed 240 pounds. Three months previously (Dec. 1, 1902), the first immunizing inoculation of weak-virulent living human tubercle bacilli, culture R1, had been administered. The dose was 0.0015 gm. intravenously. The serum was obtained twenty-four hours after bleeding.

Experiment 74.—March 19, 1903: Culture on agar of human tubercle bacilli, K1, moist growth, March 8, 1903, emulsified in normal saline, centrifuged one minute, gave a strongly opaque emulsion. Took 0.5 c.c. tubercle-bacilli emulsion, and 1.5 c.c. fresh active serums of No. 2 (normal) and Nos. 4, 5 and 6 (immunized); incubated one hour, centrifuged, decanted serums and planted four tubes each from the sediments.

CULTURE GROWTHS IN EXPERIMENT 74

Date	Serum No. 6	Serum No. 4	Serum No. 5	Serum No. 2	Control
March 24	3 good 1 contam.	1 fair 2 slight 1 neg.	Good on all	2 fair 2 slight	2 good
April 20	4 good	2 good 2 slight	Good on all	Good on all	2 good

Result.—No evidence of bactericidal influence on cultures of tubercle bacillus after treatment by calf-serums.

This experiment was repeated three weeks after the second inoculation of Calves 4, 5 and 6 with 0.025 gm. R1 tubercle bacillus.

Experiment 96.—April 2, 1903: Culture human tubercle bacilli K1 agar, March 19, 1903. Rubbed in mortar with normal sodium chlorid; centrifuged two minutes; weak emulsion. Serums fresh, active, from bleeding April 1. Took 1 c.c. emulsion: 2 c.c. each, Serums 2, 4, 5 and 6. Incubated two hours; centrifuged: A, sediment transferred to agar plates; B, part of the sediments were treated a second time for nine hours with 2 c.c. of fresh serums; then plated on agar.

April 8: A, good growth on all in microscopic colonies; no contaminations; B, slight growth in Serums 5 and 6.

Result.—No bactericidal influence clearly evident by this method.

Other attempts to demonstrate bactericidal effects on cultures were made with the culture R1 and also with virulent cultures at this time but without success. Contaminations were frequent in some tests; in most the cause of failure was the uncertainty of growth after soaking in the serums. The method was therefore limited to the use of Culture K1, which resembled the avian bacillus, though said to have been the direct descendant of Koch's first culture from human sources.

Animal inoculations of tubercle bacilli treated with Serums 2 and 6 immunized had already failed to reveal any bactericidal effect, consequently no further attempts were made with Serum 5 until repeated injections of tubercle-bacilli products over a long period had been made.

Immunized Cow 5, Injected with Water-Extracts of Tubercle Bacilli

During 1904 and 1905 large quantities of filtered water-extracts of tubercle bacilli were injected into Cow 5, both subcutaneously and intravenously. The amounts varied from 25 c.c. to 175 c.c., and frequent tests of the serum were made for specific agglutinin, precipitin and complement deviation.

The agglutination titer[11] reached only 1 to 100 and 0.025 c.c. deviated complement, but the precipitin titer was low—1 to 4.

Experiment 237.—Oct. 12, 1905; Bactericidal test by inoculation. Cow 5: weight 850 pounds. Tuberculin test, 0.5 c.c. No reaction.

November 14: Bled 100 c.c. aseptically; defibrinated with iron shavings; centrifuged 20 c.c. for serum.

B :10 c.c. defibrinated blood + 1 c.c. emulsion tubercle bacilli virulent culture human H37, Nov. 7, 1905. Four oese to 4 c.c. normal saline.

S : 5 c.c. serum only + 0.5 c.c. as before.

C : 1.5 c.c. normal saline + 1 c.c. as before.

All incubated seventeen hours; no contaminations; centrifuged; B and S diluted: B to 6 c.c.: S to 4 c.c.

November 15: Inoculated two guinea-pigs intraperitoneally with each culture as follows:

Culture	Amount Each in c.c.	No.	Weight gm.	Duration of Life, Days	Average Days
C	1.25	1	450	39	41½
		2	450	44	....
S	2	3	475	13	14½
		4	445	16	....
B	2	5	425	13	22½
		6	460	22	....

Result.—All the animals died of peritoneal tuberculosis with some generalization. The animals inoculated with blood and tubercle bacilli seemed to have a more rapid infection than the controls.

From this and other experiments we concluded that prolonged exposure of tubercle bacilli to normal (0.8 per cent.) saline solution, even in the absence of light, has a weakening action on the vitality of the tubercle bacillus.

BOVINE IMMUNIZATION WITH VIRULENT HUMAN INOCULATION

The immunization methods hitherto employed appeared to produce little effect on the serum reactions of our bovines. It was at least not evident in agglutinin, precipitin and complement-deviation tests to an extent that was expected. More virulent human bacilli were then tried with the hope of stimulating greater reaction responses to tuberculin injections and presumably bacteriolytic antibodies.

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[11] With Koch's agglutination emulsion, diluted 1 to 1,000.

To this end, Cow 5, now being full-grown and in excellent condition, weight 850 pounds, was given, Nov. 14, 1905, 0.020 gm. (moist weight) in 10 c.c. normal saline, virulent human culture H37 broth from Oct. 19, 1905, intravenously in the jugular. The highest temperature recorded in the next twenty-four hours was 102.6 F. No ill effects were noticeable, but the cow was left untreated for nearly a year except for occasional bleeding.

Cow No. 15.—A fresh cow, 2 years old, weight 650 pounds, tuberculin test negative, had also been inoculated Oct. 30, 1905, with (0.02 in 10 c.c. normal saline) virulent human culture H38 from broth Oct. 15, 1905, intravenously in the same way as Cow 5. No reaction occurred from the inoculation until the following day, when the temperature reached 103 F. at 5 p. m. Subsequently for three weeks the temperature varied from 103 to 104 F. at the same hour.

The animal gradually resumed her normal condition, but had evidently foci from the inoculation, though not a progressive infection. After a year she was given a tuberculin test simultaneously with Cow 5, and reacted to 0.5 c.c. O. T. to 41.2 C. (106 F.), indicating the persistence of some unabsorbed tubercles resulting from the inoculation. Two days after the test both Cow 15 and Cow 5 were bled for a preliminary test of the serums as to the bactericidal power.

Experiment 237 B.—Oct. 24, 1906: Bled Cows 5 and 15 two days after tuberculin test; Cow 15 reacting, Cow 5 not reacting.

October 26: Serums separated. Culture of virulent human tubercle bacilli H38 xx. Small portion rubbed in mortar + 15 c.c. normal saline, centrifuged ten minutes. Supernatant emulsion very weak and contains isolated tubercle bacilli.

A : 0.5 c.c. emulsion + 2 c.c. normal saline.

B : 0.5 c.c. emulsion + 2 c.c. active Serum 5.

C : 0.5 c.c. emulsion + 2 c.c. active Serum 15.

All incubated aseptically twenty-four hours at 37.5 C. (99.5 F.).

October 27: Centrifuged A, B and C; pipetted B and C and discarded serums; added fresh serums, respectively, Serums 5 and 15. Incubated forty-eight hours.

October 29: Repeated and incubated twenty-four hours.

November 1: Removed and pipetted all tubes without shaking them. The sediments were examined microscopically for contaminations and for evidences of lysis in the tubercle bacilli. All tubes uncontaminated; no certain evidence of lysis, although some bacilli were vacuolated.

November 1.: Inoculated all sediments into guinea-pigs, subcutaneously, right groin, as follows:

	Pig	Weight, gm.	November 30 Right Inguinal Nodes
A	1	375	Not noticeable.
B	2	335	Enlarged to size of wax bean.
C	3	310	Enlarged to size of wax bean.

December 7: Pig 1 killed thirty-seventh day. Few small nodules in lungs. No caseation in spleen and glands. Smears from spleen, tubercle bacilli negative.

December 9: Pig 3 (370 gm.) killed thirty-ninth day by tuberculin injection 0.5 c.c. O. T. Enlarged right inguinal nodes with caseation; cold abscess in groin; spleen enlarged and congested along its edge; a few tubercles seen outlined in the liver.

December 10: Pig 2 killed fortieth day; tuberculin injection, B. F.; no reaction to 0.5 c.c. In good condition; weight 370 gm. Enlarged and slightly caseous right inguinal nodes; no abscess; mesenteric nodes enlarged and caseous; spleen enlarged and beginning caseation; numerous small caseated areas in liver; none in lungs.

Result.—Clearly no evidence of bactericidal effect on the part of serums. On the contrary, the control emulsion in normal saline apparently failed to infect the animal, whereas repeated treatment with fresh active serums did not destroy enough bacilli, if any, to prevent infection, although but few bacilli were present.

Immunizing Treatment, Cows 15 and 5†*

Cow 15 was given frequent injections of tubercle bacilli water-extracts subsequent to the preceding experiments. They were injected subcutaneously and intravenously and no fever reactions were noted from 20 c.c. doses.

During the immunization of Cow 15 with water-extracts of tubercle bacilli, there was a different method tried on Cow 5. This animal gave no reaction to 0.5 c.c. O. T., Oct. 22, 1906, a year after the inoculation of virulent human tubercle bacilli. The serum agglutination titer was 1 to 33, practically that of a normal cow. Injections were therefore commenced of a preparation of tubercle bacilli residue left after extraction with water and 10 per cent. sodium chlorid followed by alcohol and ether. This residue was emulsified in normal saline, 1.0 gm. (dry) to 300 c.c., and injected in increasing doses from 1.5 c.c. to 35 c.c. subcutaneously and intravenously. Only slight reactions were produced from 25 c.c. of the emulsion subcutaneously. After three weeks' treatment the agglutinin titer reached 1 to 75. An experiment was then made with the serum in comparison with that of a healthy normal cow, using a very weak emulsion of tubercle bacilli for inoculation.

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* The agglutination titer of Serum 15 never exceeded 1 to 100, nor was any precipitin obtained. The animal was slaughtered December, 1907, and the lungs and other viscera were normal in appearance. The lung-hilus lymph-nodes were also normal except that the largest showed a white cicatrix in its center. No inoculations were made with it so that its tuberculous source could only be surmised.

† In March, 1907, some experiments were undertaken with rabbits inoculated intravenously with virulent human tubercle bacilli treated with Serums 15 and 5, and that of Cow 16 (normal), for a control, together with broth and normal saline controls. After the inoculations the ten rabbits were killed at stated intervals during the succeeding six hours with the object of studying the reaction of the tissues to the "sensitized" bacilli. The pathologic study was never made, but other observations about that time tended to diminish the interest in the result.

EXPERIMENT 237 C.—Dec. 3, 1906: *Guinea-Pig Inoculations.*—Cow 5 bled seven days after an injection of 25 c.c. residue subcutaneously, without fever reaction. Normal Cow 16 bled at the same time,

December 4: Serum agglutination test: Serum 5, 1:75; Serum 16, 1:50.

December 4: Prepared a weak emulsion of virulent human culture H39 from serum slant, Nov. 12, 1906, in normal saline centrifuged. Supernatant emulsion pipetted; tubercle bacilli scarce in smears.

Used 0.5 c.c. emulsion + No. 1 Control, 3 c.c. normal saline.

Used 0.5 c.c. emulsion + No. 2 Control, 3 c.c. Serum of Cow 16 inactivated at 65 C. (1.49 F.).

Used 0.5 c.c. emulsion + No. 3——— 3 c.c. active Cow-Serum 16.

Used 0.5 c.c. emulsion + No. 4——— 3 c.c. active Cow-Serum 5.

All incubated twenty-four hours; centrifuged Nos. 3 and 4.

December 5: Changed the serums for fresh active serums by carefully avoiding sediment in pipetting.

December 6 and 7: Same procedure as followed December 5.

December 8: Centrifuged all tubes; pipetted all except Tube 1. Added 3 c.c. normal salt solution to each tube except Tube 1. When well shaken and stirred, smears were made from each for examination. Tubercle bacilli were seldom found, but no morphologic change was seen. No contaminations noted. The contents of the tubes were then inoculated into twenty guinea-pigs, five to each series. Each tube was filled to 3.5 c.c. and 0.7 c.c. inoculated subcutaneously in the right groin of each animal.

Jan. 13, 1907: Thirty-sixth day: Inguinal nodes examined and palpated.

Series 1: No enlargement.

Series 2: Two show hyperplasia; one doubtful.

Series 3: Three show hyperplasia; two doubtful.

Series 4: All show hyperplasia.

January 15: Thirty-eighth day: One pig in each lot killed by puncture. They revealed progressively more disease from Series 1 to 4. No disease found in Series 1.

January 16: Thirty-ninth day: All the other animals were killed and compared. Series 1 revealed no tuberculous lesions to eye. Small gelatinous or translucent nodules found subpleurally in lungs of Series 3, 4 and 5. Inoculations of sections of lung into two guinea-pigs were negative after thirty-three days (nodules probably lymph-nodes).

Series 2: Pig 1, deep inguinal nodes caseated; iliac nodes slightly diseased, otherwise negative.

Pig 2, deep inguinal, iliac and lumbar nodes caseated; spleen involvement doubtful; lungs have translucent nodules as in Lot 1.

Pig 4, superficial and deep inguinal and iliac nodes caseated; lumbar nodes and spleen slightly diseased.

Pig 5 (pregnant near term), deep inguinal and iliac nodes caseated, lumbar nodes and spleen doubtful.

Series 3: Pig 1 (pregnant near term), inguinal, iliac, lumbar and lung-hilus nodes caseous; nodules beginning in spleen which is slightly enlarged.

Pig 2, same as Pig 1, only more pronounced disease in the spleen.

Pigs 3 and 4 same as 1 and 2, except beginning disease in liver. Series 3 distinctly more diseased than Series 2.

Series 4: Pigs 1, 2, 3 and 5 show marked caseation and hyperplasia of inguinal, iliac and lung-hilus nodes; enlarged and nodular spleens; beginning areas in liver and lobular, translucent areas in lung. All of this series was very uniformly diseased and distinctly advanced beyond the preceding series.

Result.—There was a definitely greater infection in animals of the immunized serum Series 5 than in the controls. A similar difference existed between the animals of the control Serum 16, active and inactive, respectively, while the saline control apparently failed to infect at all, as in previous experiments.

Discussion

It again appeared that our immunized cow-serum was more potent in favoring infection than in restraining it. The conditions of the last experiment were so carefully controlled that the accuracy of the observations was unquestionable. The interpretation of them was more puzzling. Several suggestions were considered:

1. Were the bacilli reproducing in the serums during the four days' successive incubation? This is hardly probable, as the growth in inactivated serum would have been more than in active serum presumably exerting its alexin power.

2. Did not the greater agglutinating action of the immunized cow-serum act to protect the vitality of the bacilli by coating them with agglutinins, and by reason of their clumping, render them more difficult of access to the leukocytes of the guinea-pig than single bacilli? This appeared more plausible but leaves no ground to believe that the serum plays an important part in the bacteriolysis of tubercle bacilli. The inference that cellular elements are more involved in the duty of overcoming the tubercle bacilli was plain. Our preliminary experiments with defibrinated blood (Experiment 237A) did not cover this point satisfactorily. Hence a repetition of the work seemed indicated with more care in securing tubercle bacilli free from clumps.

Guinea-Pig Inoculation with Virulent and Weak Tubercle Bacilli

Experiment 237 C2.—Feb. 1, 1907: Serum and Leukocytes. Cows 5 and 16 were bled, the former seven days after the last dose of tubercle bacilli residue, 20 c.c. The serum was separated at once from defibrinated blood and used to repeat the previous experiments, very few tubercle bacilli being employed. An emulsion of virulent culture of human tubercle bacilli, H39 serum-slant from Dec. 31, 1906, was prepared and centrifuged twelve minutes. It was diluted and the control examined for clumps before being used. Very few tubercle bacilli (1 or 2) were found in an entire smear and only rarely in clumps. With this very weak emulsion the serums were added as follows:

I

A : 0.5 c.c. control emulsion + 3 c.c. Normal saline.
B : 0.5 c.c. control emulsion + 3 c.c. Serum 5 (active).
C : 0.5 c.c. control emulsion + 3 c.c. Serum 16 (active).
D : 0.5 c.c. control emulsion + 3 c.c. Serum 5 (inactive) at 65 C.
All incubated one hour.

In addition to the preceding, an attempt to increase the virulence of tubercle bacilli was made in the following manner:

An emulsion of weak-virulent human culture R1, serum-slant from Jan. 23, 1907, was prepared in the same way and the following mixtures made:

II

A : 0.5 c.c. emulsion + 3 c.c. Normal saline.
B : 0.5 c.c. emulsion + 3 c.c. Serum 5 (active).

All tubes were incubated four successive days, those containing serums being centrifuged, pipetted and fresh serum added each day. All were centrifuged

February 5 and the serums pipetted. Before dilution smears were made of equal (measured in an opsonic pipet) quantities of the sediments to note any evidence of changes in the number and form of the bacilli.

Careful staining and examination failed to show any marked differences. In some slides no tubercle bacilli were found, in others two or three in an entire slide. Series 2 had ten to fifteen to a slide, the emulsion of R1 being stronger than H39.

To the sediments were added normal saline to make 3.5 c.c. in each tube. Thirty guinea-pigs were inoculated in series of five for each test, 0.7 c.c. being injected into the right groin.

The cows were meanwhile bled again aseptically February 2, directly into the tubercle bacilli emulsion H39 prepared the previous day, as follows:

III

A : 0.5 c.c. emulsion + 5 c.c. normal saline and 1 per cent. sodium citrate solution + 5 c.c. fresh blood from Cow No. 5.

B : 0.5 c.c. emulsion + 5 c.c. normal saline and 1 per cent. sodium citrate solution + 5 c.c. fresh blood from Cow 16.

C : 0.5 c.c. emulsion + 5 c.c. 1 per cent. sodium citrate solution (control).

After mixing and incubating six hours the blood-tubes were centrifuged, pipetted and the leukocyte layers transferred to tubes to which 1 c.c. sodium citrate solution was added to prevent coagulation. These were also incubated four days. Smears made of the final centrifuged cells showed numerous leukocytes, but few phagocyted tubercle bacilli in polynuclear leukocytes. A few extracellular tubercle bacilli but no clumps were noted in casual search in a few fields. There was no apparent contamination. The sediments were then inoculated into six guinea-pigs in series of two for each tube.

Necropsies

February 11, sixth day: *No. 4, Series I D* (Serum 5, inactive) died: Nothing abnormal found. Agar and serum-slant cultures from spleen, negative February 12.

February 12, seventh day: *No. 2, Series III A* (leukocytes) died of septicemia (?). Large brawny infiltration at site of inoculation in right groin; beginning suppuration; spleen large. Smears showed no tubercle bacilli or other organisms in pus from groin.

February 13, eighth day: *No. 4, Series II A:* died of septicemia. Right inguinal nodes normal (smears negative to tubercle bacilli); spleen and liver large and soft; hemorrhagic pericarditis; pleuritis exudativa. Infection probably antedated tubercle bacilli inoculation.

February 20, fifteenth day: Remaining animals were examined and the lymph-nodes palpated. All saline emulsion controls—I A, II A, III A and B were normal. I B, C, D, and II B serum animals showed suspicious beginning hyperplasia.

March 5, twenty-eighth day: All examined and distinct enlargement of regional lymph-nodes found in all serum and leukocyte animals. Controls II A Nos. 1, 2 and 3 were questionable.

March 9, thirty-second day: No. 4, Series I A control died of chronic septicemia; lymph-nodes normal; smears from inguinal and bronchial nodes tubercle bacilli negative; liver large, pale (fatty?); lungs show consolidation of cranial and part of caudal lobes; pregnant (3) near term. (This animal was similar to several other old guinea-pigs that were found to have recovered partially from pneumonic septicemia.)

March 16, thirty-ninth day: Seventeen animals were killed by puncture for comparison. One of Series I A, all of the Series I B, C and D and all of III A, B and C.

The controls in normal saline were all found normal. No tubercle bacilli were present in smears from the inguinal nodes.

The four guinea-pigs Series I B—(Serum 5) were all uniformly diseased with tuberculosis. Large caseous inguinal nodes; beginning caseation in iliac, retroperitoneal, bronchial and cervical chains: "hobnail" spleens with slight caseation; liver also slightly caseated; small isolated tubercles in the lungs.

Four of Series I C and three of I D were practically the same as the I B animals, except that the caseation and infiltration of lymph-nodes were less marked. (Pig 4, I D was not recorded.)

The three from Series III A and B (leukocytes) were also practically the same as the serum animals.

March 18, forty-first day: The remaining Series II A (saline control) and II B guinea-pigs were killed. They all showed slightly enlarged inguinal nodes and a few cheesy foci which contained degenerated tubercle bacilli. There were no signs of disease beyond inguinal nodes except that in one the iliac nodes were involved.

Series II B (Serum 5): Well-marked involvement of inguinal and iliac nodes with slight caseation in all; moderately enlarged spleen and occasional caseous foci in livers; lungs normal; smears from inguinal and iliac nodes reveal well-stained tubercle bacilli.

Two fresh guinea-pigs were inoculated from the iliac nodes of No. 4, II B and the spleen of No. 1, II B to note any possible increased virulence from passage after treatment by serum from Cow 5. They were both killed July 12, four months later, but were found normal. One of the first controls, Pig 2, I A (saline emulsion), was also killed at the same time (after five months) and found to have chronic tuberculosis in lymph-nodes, spleen and lungs. The other, Pig 1, I A was lost.

Results.—This experiment confirmed the results of the previous ones as to the favoring effect of immunized cow-serum on the infective power of tubercle bacilli, whether of virulent or low-virulent stocks.

The difference between the effect of active and inactive serums, while less marked than might be expected, was distinct, as was that between the immunized and normal serums. No appreciable effect was produced by the leukocytes that could not be accounted for by the influence of the plasma. There was at least no evidence of bactericidal action. The weakening influence of normal saline was again demonstrated, most of the controls being free from macroscopic disease when killed. No increase of virulence could be demonstrated in the culture R1 in the second passage as a result of serum treatment.

Discussion

The cause of the paradoxical increase of infectivity of the serum-sensitized bacilli was in itself a problem of importance and led us into further experiments to discover the cause, if possible. On the one hand we had found no multiplication of the bacilli *in vitro* and no morphologic changes. On the other hand, we knew that the bacilli were agglutinated by the serum in large clumps. It was conceivable that they were protected, as it were, with a substance which was inimical to their growth only in the body of the homologous animal, namely, the immunized cow. Unfortunately we did not have the facilities for the use of more calves. Hence we could not complete the comparison between inoculations of plain and sensitized bacilli. We therefore tried corneal inoculations in rabbits, hoping by direct inspection to observe the course of infection from day to day and thereby discover the cause of the differences.

Corneal Inoculations in Rabbits

EXPERIMENT 237 E.—March 18, 1907: Bled Cows 5, 15 and 16, seven days after injections of tubercle-bacilli residue into the first two animals.

March 19: Serum separated: Agglutination titer: Serum 5, 1 to 100 +; Serum 15, 1 to 100 ++; Serum 16, 1 to 33 to 50.

An emulsion of virulent human tubercle H38xx, serum-slant from March 7, 1907, good growth, was rubbed in 5 c.c. normal saline, centrifuged ten minutes and filtered twice through sterilized paper. The emulsion was faintly opalescent and when diluted once with equal quantities of saline gave smears with 3 to 5 tubercle bacilli to a field and clumps seldom noted. The following mixtures were made:

A: 0.5 c.c. emulsion tubercle bacilli + 5 c.c. active Cow-Serum 5.

B: 0.5 c.c. emulsion tubercle bacilli + 5 c.c. active Cow-Serum 15.

C: 0.5 c.c. emulsion tubercle bacilli + 5 c.c. active Cow-Serum 16.

D: 0.5 c.c. emulsion tubercle bacilli + 5 c.c. broth, 2.5 per cent. glycerin.

E: 0.5 c.c. emulsion tubercle bacilli + 5 c.c. hydrated chloral 1.5 per cent. solution.

F: 0.5 c.c. emulsion tubercle bacilli + 5 c.c. normal saline solution.

All incubated twenty-four hours at 38 C. (100.4 F.) and centrifuged; pipetted + 1 c.c. H_2O to each tube and transferred to small-pointed tubes.

Again centrifuged and sediment used by smearing it on a corneal knife for inoculation. Three rabbits were used for each series, A, B, C and D. Three were used for E and F in the right and left eyes, respectively. The periphery of the corneae near the nimbus was split under cocain to the width of 2 mm. for the inoculation. One animal of each series was killed after six hours and another after seven days for microscopic study (which was later abandoned for other work).

The eyes of the remaining rabbits were watched daily and showed characteristic differences. A general description will suffice to show them. During the first week the earliest to exhibit beginning disease was Series A (serum from Cow 5). Series B was practically the same, while C, D, E and F were progressively less, or had no signs whatever, as in E and F.

During the second week metastatic tubercles began to show in the corneae of A, and a well-developed focus in B and C as well. In the third week subsidence of the series A, B and C was noted, while a gradual beginning disease was observed for the first time in D, E and F.

April 16, 1907: Forty-seventh day: All killed. Relations remain unchanged. A, B and C have progressed slowly; A shows softening in each focus; B is still quite inflamed; metastases well marked; C is moderately inflamed but less than A and B; D has very slight inflammation remaining; E none; F progressive.

Necropsies revealed no internal disease except a few coccidia in two rabbits.

Result.—A confirmation of previous experiments on guinea-pigs in that the sensitized bacilli showed an accelerated infection.

The slight difference between the course of the disease in A, B and C in the rabbits' corneae raised the question anew whether or not there was any specific influence of the immunized serums on the course of infection.

The following experiment was made to test this point in part, though the result was of no great importance.

Experiment 237 F.—April 3, 1907: *Corneal inoculations in rabbits.*—Five rabbits were each inoculated in the cornea of one eye with twice the dose of twenty-four-hour sensitized bacilli with control serum than were inoculated in the other eye with Serum 5. After thirty days the control eyes showed more disease than the others. So far as this result could be applied to the question, the number of tubercle bacilli required to infect the eyes to an equal degree was less than twice the number treated with the immunized serum.

Cow 5 had no immunizing injections after March 11, 1907, until the following November. During July, four months after the last injection of tubercle bacilli residue, the serum was again tested in comparison with Control 16 by another experiment on guinea-pigs.

EXPERIMENT 237 G.—July 27, 1907: *Guinea-pig inoculations.* Cows 5 and 16 bled.

July 29: Serum separated and mixed with an emulsion of virulent tubercle bacilli. H39 slant-culture from June 12, 1907, containing four to five single bacilli to a field.

1. Took 0.5 c.c. normal saline emulsion and 3 c.c. active serum 5.
2. Took 0.5 c.c. normal saline emulsion and 3 c.c. active serum 16.
3. Took 0.5 c.c. normal saline emulsion and 3 c.c. inactive serum 16.

All incubated twenty-four hours, then to each tube 10 c.c. normal saline was added and centrifuged without stirring. The sediments were washed twice with 1 c.c. normal saline and finally diluted with 2 c.c. normal saline for inoculation. No contaminations.

Three lots each of eight guinea-pigs, were given 0.25 c.c. in the right groin. They were all killed on the forty-fourth day and the disease was fairly uniform in all. They showed enlarged and caseous regional lymph-nodes, spleen, and a few foci in the liver.

Result.—Probably little difference in the course of infection, but possibly the dose of tubercle bacilli was too large to indicate slight differences. Long cessation of treatment of the immunized cow may account for similarity to the control.

The results in the last experiment were confirmed by another eye inoculation nine months after the last treatment of Cow 5.

EXPERIMENT 237 H.—Nov. 11, 1907: *Corneal inoculations in rabbits.* Serums of Cows 5 and 16 bled Nov. 9, 1907. Four rabbits inoculated as before with twenty-four-hour sensitized bacilli H39 on opposite eyes.

Result.—After frequent observations for thirty-five days no differences were observed in the course of infection, which was gradual and mild throughout.

The injections of tubercle bacilli residue into Cow 5 were resumed Nov. 9, 1907, after a negative tuberculin test of 0.5 c.c. O. T. The doses were increased every three or four days from 5 c.c. to 35 c.c. December 20.

Another corneal inoculation was undertaken ten days later with the same technic previously described but using very few bacilli.

EXPERIMENT 237 I.—Dec. 31, 1907: *Corneal inoculations in rabbits*, with serums of Cows 5 and 16 bled December 30. Both agglutinated 1 to 50. Emulsion of H39 sensitized twenty-four hours and opposite eyes of ten rabbits were inoculated with a standard loopful of the respective sediments. Smears of one loop of each showed clumps of two to five bacilli in a field. Serum-cultures were also made but revealed no contaminations. Careful daily observations on the course of infection were recorded. The eyes of the rabbit inoculated with Serum 5 began to show inflammation first, twice as many having redness and conjunctival hyperemia in the region of the inoculation up to the tenth day. In the controls the redness was slight in seven eyes on the tenth day, while it was marked in the eyes of all but one of the rabbits inoculated with Serum 5. Seven of the latter also had distinct focal infiltration of leukocytes, but none of the controls showed it until after the tenth day.

After twenty-six days five of the Serum 5 eyes had a larger focus, pannus, or beginning ulcer. Only one of the controls was more diseased than its opposite when the experiment was terminated, the animals being killed by bleeding and puncture.

Result.—Clearly an acceleration of tuberculous infection by the inoculation of bacilli sensitized with specific serum.

The method here employed was more satisfactory in that a daily ocular inspection of the progressing disease was possible and the comparisons could be made on the same animal. The human bacillus having mild infectivity for the rabbit restricted the disease to the superior segment of the cornea and the animals betrayed discomfort only during the onset of the infection.

Period of Interrupted Immunization, Cow 5

Another year passed, during which time Cow 5 was under treatment with tubercle bacilli residue until June 11, 1908. Except for an experiment in January, 1908 (to be mentioned later), no further test of the serum was made until six months after the last treatment, when it was determined to repeat the corneal inoculation method to see if there was again a loss of specific effect.

Experiment 269.—Dec. 22, 1908: Six rabbits were inoculated with sensitized bacilli from Serums 5 and 16, using quantities of culture and technic as nearly identical with the previous test as was possible. The result after thirty days showed no perceptible difference between the eyes as to the course of disease. This confirmed our observation in 1907 that no specific effect was obtainable from Serum 5 so long after cessation of the injections of residue.

INCREASED PROTECTIVE INFLUENCE OF SENSITIZED TUBERCLE BACILLI AGAINST SUBSEQUENT INFECTION IN GUINEA-PIGS

In consideration of the enhanced infective power acquired by our weak virulent human culture R1 when sensitized by Serum 5 (Experiment 237 C2) it was of interest to observe what effect on subsequent virulent reinfection it would have. As in former experiments the R1 culture had shown a marked protection against reinfection with virulent inoculation, it was possible to expect it to be increased, or, on the other hand, it might lessen the resistance of the animals.

Cow 5 was continued under treatment from November, 1907, to June, 1908.

Experiment 263.—Jan. 8, 1908: Bled Cows 16 and 5 eight days after the last injection of 25 c.c. tubercle bacillus residue.

January 9: Serums centrifuged and added to emulsion of weak-virulent human culture R1 broth from Dec. 17, 1907, fresh growth. Took 0.030 gm. (moist) to 15 c.c. normal saline; centrifuged twenty-five minutes; 5 c.c. supernatant filtered through sterile paper and cotton several times and diluted to 10 c.c. Smears gave 5 or 6 tubercle bacilli per field.

A: 1.8 c.c. emulsion + 4 c.c. Serum 5 (active).
B: 1.8 c.c. emulsion + 4 c.c. Serum 16 (active).
C: 1.8 c.c. emulsion + 4 c.c. culture broth.

All incubated twenty-four hours; centrifuged A and B forty minutes; pipeted and replaced by 5.8 c.c. culture-broth to each; mixed all tubes thoroughly. Inoculated thirty guinea-pigs, ten for each preparation, with 0.1 c.c. in the left groin subcutaneously. Ten other pigs were selected for control to the virulent inoculation. They were then kept for three months before reinoculation.

February 10, thirty-second day: Palpated and weighed. Series A, Pigs 3 and 7, died emaciated February 4; slightly enlarged nodes in left groin; no others have palpable enlarged nodes; all but one losing weight.

Series B, Pigs 1 and 7 died in January, chronic pneumonia. No signs of tuberculosis; no enlarged nodes; all but three gaining weight.

Series C, no deaths; no palpable enlarged nodes; all have lost weight.

Series D (controls): One died of chronic pneumonia February 17; all but three losing weight.

February 17 and 18: Pig 4A and 4C died of chronic pneumonia; no other disease evident.

March 5: Pig 10A died emaciated; no disease except left inguinal nodes larger than normal.

March 6: Pigs 1 and 4D died, the former only emaciated; the latter with large submaxillary abscess.

March 19: Pigs 5 and 6C, 6 and 11D were taken for another experiment.

March 20, sixtieth day: The twenty-six remaining animals were each inoculated in the right groin with 0.3 c.c. centrifuged, filtered emulsion human tubercle bacilli H37 broth culture March 3, 1908. Smears of emulsion show from 5 to 6 per field. Practically all the guinea-pigs had gained weight except Pig 6 of Series A and Pigs 3 and 6 of Series B.

April 5: Pig 8A died emaciated; no visible disease; both inguinal chains normal.

April 29: All killed for comparison except Pig 7A and Pig 10B (suckling young).

Of the four, Series A, none had any trace of disease in the left inguinal nodes, but showed some tuberculous involvement in the right; smears were tubercle-bacilli-positive from the last, but negative in the other, and also from the iliac nodes and spleens of all this series; otherwise normal.

Of the six of Series B, two had both inguinal nodes involved; all had right; two with abscesses in the left; two in the right; one with iliac, and the spleens of three were suspicious though in two smears were negative; otherwise normal.

Of the seven of Series C, there was a close resemblance to Series B in most of them, only in one the left inguinal node being enlarged.

Of the six controls, D, all had extensive, uniformly caseous nodes, spleen and liver, the latter in the first stages. The lungs were not diseased.

Pig 10B died emaciated a month later with no visible disease. Pig 7A lived until Feb. 19, 1909, when it succumbed to advanced fibroid tuberculosis, presumably from the virulent infection.

Result.—There was a slight difference in favor of the immune serum-sensitized animals as to the extent of the infection, it being less than any of the controls. None showed the amount of disease found in the normal-serum controls, though the latter had hardly reached beyond the inguinal-iliac chain of lymph-nodes.

There was an unusually large mortality at first in this experiment from chronic pneumonia, which detracted from its value in point of numbers. The result was, however, suggestive of a specific influence in aiding the protective inoculation.

Further Immunization of Cow 5

In consideration of the low agglutination titer and complement deviation that we had obtained with Serum 5, it was determined to try larger inoculations of human bacilli followed by tubercle bacillus residue before abandoning the search for bactericidal properties in the serum.

The dangers of intravenous inoculations containing clumps of bacilli from emboli in the brain and other organs necessitated caution.

In addition to this danger, which in one of our own calves and those of other experimenters had led to tuberculous abscesses in joints, there was danger of anaphylactic shock, which at that time was well recognized as such, though formerly misinterpreted. By sedimentation and dilution we hoped to avoid the first danger, and by moderate dosage, the second. In this we were successful, and during the next two years Cow 5 received four more inoculations of living, virulent human bacilli H37 besides intervening treatment with tubercle bacilli residue and other tuberculins.

The dates of inoculations were as follows:

Dec. 29, 1908: Third inoculation; 10 c.c. centrifuged emulsion, estimated (by deducting sediment) 0.060 gm.

August 5, 1910: Fourth inoculation; 25 c.c. centrifuged emulsion, estimated as previously, 0.170 gm.

Sept. 20, 1910: Fifth inoculation; 25 c.c. centrifuged emulsion, same estimation, 0.175 gm.

Dec. 30, 1910: Sixth inoculation; 25 c.c. centrifuged emulsion, estimated as before, 0.130 gm.

Fever reactions from 103 to 106 F. followed each dose within six hours, but subsided on the next day. The cow remained in fine flesh and condition throughout the further treatment, yet no reactions resulted from subcutaneous tuberculin injections of various kinds. Feb. 1, 1911, 1 c.c. O. T. diluted was given intravenously. There was respiratory embarrassment for ten minutes followed by a fever to 105.6 in six hours. Feb. 7, 1911, 1.5 c.c. O. T. was given in the same way. Marked difficulty and acceleration of respiration followed, with dizziness and a temperature of 104.5 in six hours.

The symptoms of anaphylaxis were too well marked to permit further intravenous injections. Further subcutaneous injections of W. E. and T. O. were given, but produced no higher agglutination titer than 1 to 100. A slight precipitation reaction was obtainable. The complement deviation was also found no lower in many tests with the same stock antigen. The titer during 1910 and 1911 was 0.02 c.c. serum to completely absorb complement with 0.1 c.c. T. R. emulsion (0.001 gm. dry to 1 c.c.). Considering the unpromising outlook for a higher grade of antibodies the immunization was discontinued April 27, 1911.[13] The animal was still in perfect condition when slaughtered in December, 1912. Very unfortunately no post-mortem examination was feasible, as she was kept at a distance from the town.

Final Experiments to Test Bactericidal Effect of Serum, Cow 5

Experiment 206 A.—June 23, 1909: *Subcutaneous Inoculations.* Six months after the third reinoculation, during which time continuous treatment with tubercle bacilli residue was carried on. Bled Cows 5 and 16.

July 27: Incubated with emulsion virulent human culture H41 (prepared as in previous experiments) four days without change. Centrifuged; inoculated subcutaneously into five pigs for each test in right inguinal region. Serum 5 animals died sooner than those of Serum 16, the average being 36.2 days as compared with 55.2 days for the controls.

The Serum 5 animals emaciated and revealed disease in the inguinal and iliac nodes with caseation or beginning abscess. One survived three months and had an abscess in the groin with spleen and lungs involved. The controls that survived longer had more disease and three showed caseous nodes and foci in the spleen.

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[13] It must be confessed that we dropped this work at this point because other things seemed more important, and it was impossible to keep large animals near the laboratory with our limited facilities.

Result.—No specific effect of Serum 5 was demonstrated in this experiment unless the shorter average lifetime of the Serum 5 animals may be ascribed to some toxic action produced by the serum acting on the tubercle bacilli and which was liberated in the animals. The animals were in poor condition at any rate.

A final attempt to show a bactericidal influence of Serum 5 was made a month after the sixth and last inoculation, and a week after a tuberculin reaction on Feb. 1, 1911.

EXPERIMENT 206 B.—Feb. 7, 1911: *Intracutaneous inoculations.* A different method was tried in this experiment by comparing intracutaneous inoculations made on the same animal simultaneously. A new normal cow was used for control serum, and both active and inactive serums used, together with a broth control. Opposite sides of six guinea-pigs were shaven and the inoculations made after three days' incubation with human tubercle bacilli H37. The inoculations were made sufficiently far apart to cause any marked difference in the reactions to be noticeable. The infections were practically the same up to the nineteenth day, when all but the broth-controls began to show caseous centers. The Serum 5 (active) seemed more inclined to ulcerate than the rest, yet the infiltration and redness were practically alike. At this time no lymph-nodes showed enlargement. As no certain differences were assured the animals were soon killed.

Result.—No evidence of specific action from Serum 5 in this experiment.

DISCUSSION

The general effect noted throughout the foregoing experiments was unfavorable so far as any practical value of the immunized cow-serum in the therapy of tuberculosis.

The sensitized living bacilli which we hoped might be weakened by the serum were in fact rather more infective and therefore less available for vaccines.

The phenomenon of increased infectivity was associated with serums from the cow under active immunization with T. R. During resting periods the serum lost its property for the time, but soon regained it when the injections of T. R. were resumed. The antibody reactions were never strong, and the agglutination was the most delicate and pronounced of any. The serum titer was, notwithstanding, often no higher than that from a normal cow, so that it was difficult to understand that the difference in infectivity was due to the greater agglutination. Considering the claim that serum-sensitized B. E. tuberculin is more easily absorbed than the plain emulsion, one may account for the increased virulence produced in guinea-pigs and rabbits by the bacteriotropic effect of the serum on living bacilli as well as by the agglutination.

It may be that specific agglutinins and bacteriotropins excite a more active phagocytosis under these conditions. The leukocytes ingest large clumps of agglutinated bacilli which they are unable to dispose of. In the non-sensitized bacilli they find them in singles and can weaken or kill them more readily. As a working theory the preceding explanation, partly mechanical as well as biological, may account for our results. In many other pathogenic organisms one may note rapid lysis under the influence of antiserums or in similarly sensitized bacteria when inoculated. Even were an active lysin present in our cow-serums the difficult solubility of the tubercle bacilli undoubtedly masks it.

It has in fact been suggested that by prolonged digestion of living tubercle bacilli in active immune serums (as in our experiments) the weaker bacilli are devitalized, if not dissolved, leaving only the most vigorous and resistant ones. The latter when inoculated, being clumped together, are able to survive the cellular digestion longer. In these ways one may explain the seeming paradox in our results and the causes for the earlier reaction and further spread of the disease in the inoculated animals.

Intracellular digestion of tubercle bacilli is slow when observed in the peritoneal exudate of previously infected animals. It is much slower in control animals and few observers have claimed to dissolve them at all in immune serum *in vitro*. The peculiarity of the wax in tubercle bacilli places this organism in a class by itself as unusually resistant against lysis. Under the most favorable conditions for the lysis of tubercle bacilli a few often escape and may produce an infection; hence the difficulty of experimental demonstration of the mechanism.

Some consideration should be given to the possible influence of the cow-serum as such in our experiments. In most cases it was washed out of the prepared bacilli and only the antibody fixed to the bacilli could come into the question. There is no reason to think that it caused any aggravation of the infection, except through the anchored antibody. It is true that other observers (Calmette and Guérin[14]) have found that immunized cow-serum aggravated the disease in guinea-pigs, though in a recent tentative experiment Rothe and Bierbaum[15] on two guinea-pigs thought that 0.1 to 0.2 c.c. immunized cow-serum mixed with tubercle bacilli twenty hours weakened the infection. Immunized cow-, horse- and mule-serum were found by Ruppel and Rickman[16] to restrain infection in guinea-pigs by injections of 5 c.c., though it is not stated which serum was used, nor have further details been published.

Nearly all of the earlier experiments were with repeated injections of horse-serum or that of other immunized animals: Bâbes and Proca,[17]

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[14] Calmette and Guérin: Ann. d. l'Inst. Pasteur, 1911, xxv, 626.

[15] Rothe, E., and Bierbaum, K.: Veröffentl. d. Robert Koch Stiftung 1913, Nos. 8, 9, p. 169.

[16] Ruppel and Rickman: Ztschr. f. Immunitäasforsch., 1910, vi, 383.

[17] Bâbes, V., and Proca, G.: Ztschr. f. Hyg. u. Infectionskrankh., 1896, xxiii, No. 3, p. 331.

Karwacki.[18] They were usually harmful because of the anaphylactic sensitization produced, which at the time was not understood.

In all these experiments with antituberculous serums it must also be remembered that an anaphylactic antibody to tuberculo-protein must frequently be present in the serum. This might be a source of slow poisoning to a tuberculous animal by acting on the bacilli and setting free small amounts of anaphylatoxin. It is conceivable that the early reaction and greater irritation of the rabbit cornea seen in our experiments with immune-serum-sensitized bacilli were due to this cause. The probability of this is lessened by the fact that the poison would have been equally strong, if not stronger, from the bacilli sensitized with inactivated than with the active serum.

To recapitulate the conclusions of most importance, the following summary may be presented:

SUMMARY

1. The foregoing experiments relate to the properties of the serum of a cow repeatedly immunized against tuberculosis during a period of ten years.

2. Six intravenous inoculations of living human cultures of tubercle bacilli, both of virulent and weak-virulent infectivity, besides numerous injections of all forms of tuberculin, were given to this cow.

3. Specific agglutinin, precipitin, opsonin, and complement-deviating antibody were demonstrated in varying degree in the serum but never reached a high content.

4. The presence of a bacteriolysin was not demonstrated; neither was a bacillicidal effect recognized either in the serum or leukocytes.

5. Living human tubercle bacilli "sensitized" with the immune serum showed increased infective power in guinea-pigs and rabbits as compared with normal cow-serum.

6. The increased infective power was manifested by earlier and more marked reactions or inflammation following inoculation, and a wider spread of the disease than in controls.

7. This acceleration of infection was not manifest unless the cow had recently received injections of pulverized bacillus residue, but the immune-serum-agglutinin titer was not always greater than the normal cow serum.

8. To explain the apparent paradoxical action of the immune serum, it is suggested that the strongly agglutinated bacilli were protected from injury by the leukocytes of the inoculated animal by reason of the clumping. The bacilli were presumably phagocyted in large masses but more difficult of digestion for that reason. It may also be suggested that the

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[18] Karwacki, L.: Ztschr. f. Tuberk., 1906, viii. 52-59.

bacilli laden with antibody (opsonin) were more rapidly phagocyted and scattered, but owing to the resistant wax were not digested in sufficient numbers. ,

9. A "sensitized" *living* tubercle-bacillus vaccine is not safe or practicable when prepared from immune bovine serums, considering the above-mentioned results.

My heartiest acknowledgements are due, especially to Dr. Joseph L. Nichols, Dr. J. Woods Price, and the late Dr. Albert H. Allen, who assisted in these studies.

The expense of this work was borne by Mrs. A. A. Anderson of New York City, to whom we also owe our thanks.

AN EXPERIMENTAL STUDY OF INTESTINAL OBSTRUCTION *

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Intestinal obstruction in man, if unrelieved, speedily causes death. The fatal outcome is too rapid to be the result of starvation, and three general theories have been advanced to explain it:

1. A disorder of the nervous mechanism controlling the cardiac and vasomotor systems.

2. A bacterial infection of the organism by the passage outward of bacteria from the intestinal lumen.

3. An intoxication from poisonous substances imprisoned in the intestine orally to the obstruction.

Two modifications of the last theory have recently come into prominence. The first was originally advanced by Vidal,[1] and more recently elaborated by Maury Draper[2] (formerly Draper Maury), in which the presence of a substance in the upper intestinal tract was believed to exist, which, unless neutralized by substances elaborated lower down, entered the system as a poison.

The second modification is advanced by Whipple, Stone and Bernheim.[3] These workers believe that stagnation of the duodenal contents results in the formation of a severe poison, which readily enters the system, and produces death. This poison may be obtained from the mucosal cells of the duodenum as well as from the duodenal contents.

THE THEORY OF A NERVOUS DISORDER

In favor of this theory, clinical evidence has been adduced. The tachycardia, the low blood-pressure, the profound collapse of the patient,

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* Preliminary reports on the work here detailed have appeared in Am. Jour. Med. Sc., March, 1912, p. 357; Jour. Am. Med. Assn., 1912, lix, 82; Jour. Exper. Med., 1913, xviii, No. 2, p. 139. These reports are freely abstracted in the present article in order to present the subject in its entirety.

[1] Vidal: Rev. de chir., 1900, xxvi, 521; Cong. Franc. de chir., 1905, xxviii, 1237.

[2] Draper, J. W.: Experimental Intestinal Obstruction, Jour. Am. Med. Assn., 1911, lvii, 1338; John Hopkins Hosp. Bull., 1909, xx, 184; Am. Jour. Med. Sc., 1909, cxxxvii, 725; Death in Acute Intestinal Obstruction and Kindred Conditions Is Due to Physiologic Disturbance, Jour. Am. Med. Assn., 1910, liv, 5.

[3] Whipple, Stone and Bernheim: Jour. Exper. Med., 1913, xvii, No. 3, p. 286.

and the wide dilatation of the splanchnic blood-vessels, all point to a loss of activity on the part of the medullary nerve-centers. The early writers saw in these the results of a reflex disturbance from stimuli acting on the nerve endings in the intestinal wall. It is undoubtedly true, however, that exactly this train of events may arise from a toxemia or a bacteriemia without the intervention of any afferent nerve impulses.

Recently, Braun and Boruttau[4] have modified this theory somewhat, and assign the above-described symptoms to a disturbance of the circulation resulting from interference, chiefly mechanical, with the inherent nerve plexuses in the intestinal wall. They see a parallel between a gradual bleeding to death and the death in intestinal obstruction. The loss of body fluids resulting from failure of absorption, the enormous outflow of fluid into the intestine, the persistent vomiting, and the stagnation of blood in the splanchnic area lead to an anemia of the brain-centers which progresses till these centers cease their activity, and death results. They experimented most exhaustively on rabbits to support this view, but the evidence is all indirect, and seems to us not to amount to a proof of the theory. We are unable to find in the literature any convincing experimental work that the nervous system is primarily at fault. Certainly, as death approaches, there is a profound disturbance of the nervous control of the heart, blood-vessels and respiration. but this, we believe, is in no sense a reflex disturbance, nor the result of an anemia, *per se,* of the nerve-centers. It differs in no way from the last stages of any severe sickness which is progressing toward a fatal issue. The loss of body fluids is a matter of the utmost importance, but not because of its effect in producing a brain anemia.

THE THEORY OF BACTERIAL INFECTION

The infection theory has much more to support it. The intestinal lumen is the normal habitat of innumerable micro-organisms which are potentially pathogenic. When an obstruction exists, these no longer have their normal outlet per anum. They are dammed up in the intestine under favorable conditions for their growth (McClure[5]). The damage to the intestinal mucosa may allow their passage outward, either into the blood-stream, lymphatics, or directly into the peritoneal cavity. Proof of this possibility is seen clinically in the presence of a peritonitis as a complication of intestinal obstruction without perforation; also in the frequent finding of colon bacillus in the blood as a pathogenic micro-organism, under very varied conditions of intestinal disturbances less severe than an obstruction, and in the bacteriemia from the *Bacillus typhosus* when the intestine is ulcerated by the action of that organism.

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[4] Braun and Boruttau: Deutsch. Ztschr. f. Chir., 1908, xcvi, 544.

[5] McClure, R. D.: An Experimental Study of Internal Obstruction, Jour. Am. Med. Assn., 1907, xlix, 1003.

Von Khantz,[6] experimenting on rabbits in a low intestinal obstruction, often found a bacterial invasion of the blood and the peritoneum, but never the former without the latter. Borszesky and von Genersich,[7] on the other hand, found a blood infection with no invasion of the peritoneum. There can be no doubt that a bacterial invasion of both the peritoneum and the blood may take place in intestinal obstruction, but it is not an essential accompaniment. It occurs late as a complication, often a terminal one. Both clinically and experimentally it will result most often when the obstruction is complicated by a strangulation. Without this complication, intestinal obstruction will kill with no passage of bacteria beyond the intestinal wall.

Tables 1 and 2 give the results of our experiments bearing on this point. In the first series the obstruction was produced by dividing the intestine from 10 to 30 cm. below the pylorus, and closing the ends by inversion. It will be noted that in all these cases some micro-organisms were found in the organs examined. This, we believe, was due to the fact that all the examinations were made several hours post mortem, because all the animals died during the night, and possibly to a local soiling at the site of operation. In the second series, however, the obstruction was produced by the clamp described below, and the animals were either killed when it was believed they were too sick to live over night, and immediately examined, or examined very soon after death occurred from the obstruction itself. This series of seven cases furnishes irrefutable proof that death results from an obstruction of the upper intestine in the dog, without any invasion of the peritoneum, blood, liver or spleen by bacteria, which are demonstrable by the methods employed. The methods in the two series were exactly similar and their efficiency in detecting organisms is amply demonstrated in the first. The cultures were taken at autopsy on slant agar or Loeffler blood-serum, or both. Usually four tubes, sometimes only three of each, were inoculated from each tissue, and grown under both aerobic and anaerobic conditions at incubator temperature. For the anaerobes the Buchner method or the Cornell modification of it was used. The tubes were examined at the end of one, two and three days. All the cultures were made in the sterile room of the Cornell bacteriology laboratory. This consists of a closed cabinet, ventilated through a bacteria-proof filter, in the roof of which is suspended an ordinary revolving lawn-sprinkler. The water is turned through this for fifteen or twenty minutes prior to taking the cultures. Thus the air is mechanically sterilized by washing out the micro-organisms. All the needed apparatus for taking the cultures and smears is assembled before beginning the inoculations,

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6. Von Khantz: Arch. f. klin. Chir., 1909, xxxviii, 412.
7. Borszesky and von Genersich: Beitr. z. klin. Chir., 1902, xxxvi, 448.

and the air-tight door is kept closed until all cultures are completed. The technic in making the inoculations is that usually employed in obtaining cultures from post-mortem material. The efficiency of the room and the method is demonstrated by the fact that only three air contaminations were found in several hundred tubes.

In some of the later cases of the second series no cultures were taken from the spleen, since it was noted that this organ never showed infection when the liver and peritoneum were without infection. Often, too, the spleen cultures gave no growth when the other organs were actively infected. A summary of this series shows that the femoral blood was cultured seven times, and always was without growth; the liver was cultured six times, and showed one colony of Gram-positive cocci, in one tube of one case, probably an air contamination; the results from the peritoneal cultures were exactly the same as from the liver; the spleen was cultured only twice, with negative findings both times; the jejunal or duodenal contents above the clamp were cultured seven times, and all tubes showed an abundant growth of various microorganisms.

TABLE 1.—CULTURES FROM ORGANS OF ANIMALS WITH INTESTINAL OBSTRUCTIONS, SERIES 1

Case	Organs	Cultures Taken	Tubes Showing Cocci	Tubes Showing Bacilli	Characteristics	Remarks
12	Spleen	2 aerobic 3 anaerobic	None	1 aerobic 2 anaerobic	Morphology and growth characteristic of colon bacillus on usual differential mediums.	Intestine sectioned and closed 34 cm.. distal to pylorus. Lived 80 hours. Cultures taken 10 hours post mortem
	Liver	2 aerobic 4 anaerobic	All	All	(1) Gram + coccus. (2) Bacillus identified as colon on differential mediums. (3) Also very many colonies of a large Gram + anaerobic bacillus with morphology of *Bacillus aërogenes capsulatus.*	
	Jejunum	2 aerobic 4 anaerobic	All	All	(1) Gram + coccus. (2) Large anaerobic Gram + bacillus. (3) Gram — bacillus of two kinds, first long and slender; second. short and plump. Both grew in anaerobic tubes, while the former only grew in aerobic tubes.	
13	Femoral blood	4 each	None	None	....	Intestine sectioned 36 cm. from pylorus and ends closed. Autopsy about 13 hours post mortem.
	Peritoneum	4 each	All	None	(1) Gram + and (2) Gram — coccus.	
	Spleen	4 aerobic 3 anaerobic	1 aerobic	None	Gram + coccus. Same organism as in peritoneum.	
	Liver	4 each	None	None		
	Jejunum	4 each	All	All	Same as in Case 12.	Cultures taken from jejunum when it was sectioned at operation gave the same results as at autopsy.

TABLE 1.—CONTINUED

Case	Organs	Cultures Taken	Tubes Showing Cocci	Tubes Showing Bacilli	Characteristics	Remarks.
14	Jejunum at operation	2 aerobic 2 anaerobic	All	All	(1) Gram — bacillus. (2) Gram + coccus. (3) Large Gram + bacillus.	Intestine sutured after section 31 cm. from pylorus. Autopsy 36 hours post mortem.
	Jejunum at autopsy	4 each	All	All	(1) Anaerobic gas-forming Gram — bacillus. (2) Gram + bacillus. (3) Gram + coccus.	
	Femoral blood	4 each	2 aerobic	All	(1) Gram + coccus. ferments lactose, and glucose, without gas. no change in neutral red and saffranin. (2) Large anaerobic Gram + bacillus with morphology of aerogenes capsulatus bacillus.	
	Peritoneum	2 each	All	All	(1) Gram + coccus. same as in femoral blood. (2) Gram — bacillus-like colon bacillus.	
	Spleen	4 each	2 aerobic	2 anaerobic	(1) Gram — coccus. (2) Gram — bacillus having the characteristics of colon bacillus.	
	Liver	2 anaerobic 4 aerobic	2 anaerobic 3 aerobic	None	(1) Gram + coccus as in peritoneum and femoral blood.	
15	Jejunum at operation	4 each	4 anaerobic	4 anaerobic 2 aerobic	Gram — bacillus, mobile same as in peritoneum.	Intestine ligated with tape 35 cm. from pylorus. Autopsy 4 hrs. post mortem. General peritonitis present.
	Jejunum at autopsy	4 each	1 anaerobic	All		
	Peritoneum	4 each	4 anaerobic	All	(1) Gram — bacillus having characteristics of colon bacillus (2) Gram — bacillus intermediate in colon group, changes neutral red and saffranin. does not ferment lactose. (3) Gram + coccus.	
	Femoral blood	4 each	None	None		
	Spleen	4 each	None	None		
	Liver	4 each	None	None		
16	Jejunum at operation	4 each	....	All	Not identified.	Bowel sectioned and inverted 48 cm. from pylorus. Lived about 32 hours. Autopsy 12 hours post mortem. No peritonitis.
	Jejunum at autopsy	4 each	All	All	(1) Short Gram — bacillus. (2) Gram + coccus resembling streptococcus. (3) Large Gram + bacillus.	
	Femoral blood	4 each	None	None		
	Spleen	4 each	None	None		
	Liver	4 each	All	All	Gram — short, stout. bacillus mobile (2 strains), resembling colon bacillus. (2) Gram + bacillus. (3) Gram + coccus.	
	Peritoneum	4 each	All	All	(1) Gram + coccus. (2) Gram + bacillus. (3) Gram — bacillus. short and stout. mobile. Same as in liver	

TABLE 1.—CONTINUED

Case	Organs	Cultures Taken	Tubes Showing Cocci	Tubes Showing Bacilli	Characteristics	Remarks
17	Jejunum at autopsy	None taken	None taken	....	....	Jejunum clamped 37 cm. from pylorus with Crile clamp, which at autopsy was found to have cut through. Autopsy 8 hours post mortem, lived about 88 hrs. General peritonitis present.
	Femoral blood	4 each	None	None		
	Spleen	4 each	1 anaerobic	None	Gram + coccus. One colony outside line of inoculation. Probable air contamination.	
	Liver	4 each	None	None		
	Peritoneum	4 each	4 anaerobic 3 aerobic	4 anaerobic 3 aerobic	(1) Gram — bacillus, having characteristics of coli communis. (2) Gram + coccus. (3) Gram + bacillus short and fat and growing in long chains.	
18	Jejunum	None taken	....	....	....	Jejunum clamped with Crile clamp 20 cm. from pylorus. Killed with chloroform 91 hrs. after operation. Clamp cut through, local peritonitis resulting.
	Femoral blood	4 each	None	None	(1) Gram — bacillus.	
	Peritoneum	4 each	None	All	(2) Gram + bacillus.	

TABLE 2.—CULTURES FROM ORGANS OF ANIMALS WITH INTESTINAL OBSTRUCTIONS, SERIES 2

Case	Organs	Cultures Taken	Tubes Showing Cocci	Tubes Showing Bacilli	Characteristics	Remarks
19	Jejunum	3 aerobic 3 anaerobic	3 anaerobic	3 anaerobic 3 aerobic	(1) Gram — bacillus. (2) Gram + bacillus	Intestine occluded with special clamp 18 cm. from pylorus. Lived 172 hrs. after operation. Killed with chloroform. Autopsy immediately. No peritonitis; local abscess around clamp.
	Femoral blood	4 aerobic 3 anaerobic	None	None		
	Spleen	4 aerobic 4 anaerobic	None	None		
	Liver	4 aerobic 3 anaerobic	None	None		
	Peritoneum	3 anaerobic 4 aerobic	None	None		
	Abscess around clamp	2 aerobic 2 anaerobic	....	1 anaerobic 2 aerobic	Gram — bacillus.	
20	Jejunum	None taken	....	....	....	Occlusion clamp 16 cm. from pylorus. Lived 90 hrs. Died. Autopsy. No peritonitis.
	Femoral blood	4 aerobic 4 anaerobic	None	None		
	Liver	4 anaerobic 4 aerobic	None	None		
	Peritoneum	4 aerobic 4 anaerobic	None	None		
	Exudate around clamp	3 aerobic 3 anaerobic	None	None		
21	Jejunum	4 aerobic 4 anaerobic	4 anaerobic 4 aerobic	4 anaerobic 4 aerobic	(1) Gram + coccus. (2) Gram + bacillus. (3) Gram — bacillus	Occlusion clamp on jejunum 16 cm. from pylorus. Dog lived 58 hrs. Autopsy 8 hrs. post mortem. Peritoneum clean.
	Femoral blood	4 aerobic 4 anaerobic	None	None		
	Spleen	4 aerobic 4 anaerobic	None	None		
	Liver	4 aerobic 4 anaerobic	None	None		
	Peritoneum	3 aerobic 4 anaerobic	1 aerobic	....	Gram + coccus. One colony only, probably air contamination.	

TABLE 2.—CONTINUED

Case	Organs	Cultures Taken	Tubes Showing Cocci	Tubes Showing Bacilli	Characteristics	Remarks
22	Jejunum	3 aerobic 3 anaerobic	2 aerobic 1 anaerobic	....	Gram + cocci.	Occlusion clamp 12 cm. from pylorus. Lived 21 days. Killed with ether. Clamp not absolutely tight. No peritonitis.
	Femoral blood	4 aerobic 4 anaerobic	None	None		
	Liver	3 aerobic 3 anaerobic	None	None		
	Peritoneum	4 aerobic 4 anaerobic	None	None		
23	Jejunum Liver	None taken None taken	....	....	....	Occlusion clamp 12 cm. from pylorus. Lived 240 hrs. Killed with cyanid and autopsied immediately. No peritonitis. Clamp tight.
	Femoral blood	3 aerobic 4 anaerobic	None	None		
	Peritoneum	4 aerobic 4 anaerobic	None	None		
24	Jejunum	2 aerobic 2 anaerobic	None	2 aerobic 2 anaerobic	Gram + and — bacilli	Occlusion clamp 16 cm. from pylorus. Lived 205 hrs. Autopsied 2 hrs. post mortem. No peritonitis. Small abscess around clamp was tight.
	Femoral blood	3 aerobic 4 anaerobic	None	None		
	Liver	4 aerobic 4 anaerobic	None	None		
	Peritoneum	4 aerobic 4 anaerobic	None	None		
	Clamp abscess	2 aerobic 2 anaerobic	2 anaerobic 2 aerobic	None	Pure growth of Gram + coccus.	Occlusion clamp 16 cm. from pylorus. Lived 240 hrs. Killed with ether. Autopsy immediate. No peritonitis.
26	Jejunum	4 aerobic 4 anaerobic	.... None	4 aerobic 4 anaerobic	(1) Small Gram — bacillus. (2) Large, long Gram + bacillus.	
	Femoral blood	4 aerobic 4 anaerobic	None	None		
	Liver	3 aerobic 4 anaerobic	1 aerobic	None	One colony outside inoculation of a Gram + coccus.	
	Peritoneum	4 aerobic 4 anaerobic	None	None		
28	Jejunum	2 aerobic 2 anaerobic	2 anaerobic	2 aerobic 2 anaerobic	Gram + and — bacilli and cocci. Anaerobic tubes show gas production.	Occlusion clamp 11 cm. from pylorus. Lived 56 hrs. Autopsy 10 hrs. post mortem. Abscess around clamp. No peritonitis. Clamp tight.
	Femoral blood	4 aerobic 4 anaerobic	None	None		
	Liver	4 aerobic 3 anaerobic	None	None		
	Peritoneum	4 aerobic 4 anaerobic	None	None		
	Clamp abscess	2 aerobic 2 anaerobic	None	None		

Case 22, given in Table 2, is not included in the summary because the obstruction was not complete. It is worthy of note here, however, that the jejunal tube only showed a growth of a Gram-positive coccus in one-half the tubes inoculated, showing that the long period (twenty-one days) with only sterile water by mouth did much toward sterilizing the upper bowel.

It is thus demonstrated that no matter what the rôle of the microorganisms may be within the bowel, or no matter how active they may sometimes become in causing complications by penetration of the bowel into the general system, this is not a necessary factor either in causing the symptoms of the disease or in determining the fatal outcome. The theory, therefore, which holds a bacteriemia as the responsible factor in the death following intestinal obstruction is untenable.

THE INTOXICATION THEORY

This theory, on the contrary, has experimental evidence to support it, and no experiments have proved the absence of a toxemia. Clairmont and Ranzi[8] demonstrated that the stagnated material above an obstruction, after passage through a Reichel or Pukal filter, was exceedingly toxic when injected into the blood of an animal. Kukula[9] found a toxic material in the alcoholic extracts of the intestinal contents in experimental ileus. Roger,[10] and Roger and Garnier,[11] went farther and proved that the normal content of both the stomach and the intestine are poisonous when thus injected. They did not filter it, but death occurred too early to be the result of an infection. The toxicity was only one-third as great when injected into the portal vein as when injected into a peripheral vein. They also injected it into a mesenteric artery, against the current, so that it was carried backward and then redistributed through branches to a considerable section of the intestine. Here it produced emboli and stopped the absorption, so that large doses were not fatal.

Murphy and Vincent[12] found that the material from the obstructed or strangulated intestine was very poisonous when injected into the peritoneal cavity, and that its poisonous properties were destroyed by boiling or passage through a Berkefeld filter. They concluded, therefore, that living bacteria are the important factors. It does not seem to us that this conclusion is tenable. Their experiments only prove that living bacteria, if they obtain entrance into the peritoneum, will kill.

Whipple, Stone and Bernheim[3] worked with a material obtained from the doubly occluded duodenum, and determined that it was very poisonous even after being rendered sterile. They also found what they believed to be the same poison in the mucosa of this part of the intestine, when one end of it was closed and the other end allowed to drain externally. They applied their results to a simple intestinal obstruction, and concluded that death in this condition is caused by a poison arising from the duodenal mucosa. Their views are opposed in important particulars to the results obtained by us, and will receive closer study later. In general it may be stated that the symptoms arising from the injection of intestinal contents into the blood, as reported, differ very markedly from those appearing in the obstructed animal, and there are many objections, as pointed out by Guibe,[13] Braun and Boruttau,[4] Korentchevsky,[14] and others, against accepting these experiments as directly bearing on the cause of death in intestinal obstruction. The lessened absorption from the obstructed intestine is one objection offered. Clairmont and Ranzi[8] found that potassium iodid placed in the bowel above the obstruction was excreted from the kidneys in greater quantities than normal, up to eight or ten hours after the obstruction was produced; the excretion rapidly decreased after that, and came to a stop in about fifteen hours.

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[8] Clairmont and Ranzi: Arch. f. klin. Chir., 1904, lxxiii, 696.

[9] Kukula: Arch. f. klin. Chir., 1901, lxiii, 773.

[10] Roger: Rev. Scient., 1907, xlv, 65; Presse méd., 1911, xix, 1.

[11] Roger and Garnier: Arch. de méd. expér., July, 1906; Rev. de méd., 1906, xxvi, 609; Presse méd., 1906, xiv, 325.

[12] Murphy and Vincent: Boston Med. and Surg. Jour., 1911, clxv, 684.

Braun and Boruttau[4] gave strychnin to their obstructed animals, and from the resulting symptoms they concluded that absorption became markedly reduced from the start. On this experiment they base their chief objection to the intoxication theory. A more important objection to the use of the evidence of the injection experiments as a proof of the intoxication theory is that many substances injected directly into the circulation are poisonous, whereas, if they have to pass through living cells to get into the blood, their poisonous properties are entirely destroyed. Peptone is such a substance, and is a good illustration in this connection. The injection of peptone into the blood produces symptoms of poisoning, which may end in death. The absorption of peptone from the intestine is, on the contrary, a normal physiologic process. Therefore, the mere presence in the obstructed intestinal tract of substances which act as poisons when injected into the blood is no indication that these substances cause the death resulting from an obstruction, since such substances may be normally found in the intestine in conditions of continued health. To accept the view that such a death results from a toxemia it must be conceived either that new poisons are elaborated and absorbed or that an abnormal absorption of the poisons normally takes place.

In undertaking our work, after a study of the literature, we tentatively accepted the first hypothesis and planned our experiments to determine by a process of exclusion from what sources conception was forced on us, namely, *that the essential factor in causing the symptoms and death in intestinal obstruction does not lie in the poisons per se, but in the production of lesions which favor their abnormal absorption, and lacking these lesions the animals die only from dehydration, or starvation if dehydration is prevented.* We believe our reader will get a clearer understanding of our findings if he will follow, step by step, the reasoning and experiments which led to this change of conception in our minds.

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[13] Guibe: Presse méd., 1909, xvii, 233.

[14] Korentchevsky: Roussky Vratsch, 1908, p. 1572. (Cited by Guibe, Note 13).

In searching for the source of the poison we accepted three possibilities: (1) foodstuffs or substances derived from them; (2) secretory substances from the alimentary tract and digestive glands, or their derivatives; (3) true bacterial toxins. It was our intention to exclude one after the other of these possible sources and study the conditions resulting after an obstruction was produced. It is readily seen that there may enter into all of these the result of bacterial activity. While, as detailed above, our bacterial studies showed that a bacteriemia is not necesasrily present, they did not exclude either a bacterial toxin or substances developed by virtue of the presence of bacteria in the occluded bowel.

EXPERIMENTS TO DETERMINE THE EFFECT OF FOODSTUFFS OR THEIR DERIVATIVES ABOVE THE POINT OF OBSTRUCTION

All animals were fully etherized before the operation. No food was given in any case after the operation, unless so stated. Water, however, was given freely, unless otherwise noted.

Experiment 3.—A cat which had received no food for ninety-six hours before operation. Duodenum sectioned and ends closed by inversion 10 cm. below pylorus. For three days the animal remained in good condition. Vomited. Fourth day showed weakness and some rigidity of muscles of extremities. Just before death had convulsions involving extremities. Killed with chloroform ninety-six hours after obstruction. Autopsy immediate. No peritonitis. Closure of bowel ends tight. Stomach contained small amount of normal-appearing gastric content. Duodenum empty. Neither stomach or duodenum was distended.

Experiment 4.—Fox terrier. Fed twenty hours before operation. Repetition of Experiment 3, the section being 11 cm. distal to the pylorus. Except for some weakness and vomiting, seemed like normal dog for four days. Died with progressive weakness and vomiting on the seventh day. Autopsy. No intestinal leakage. No peritonitis. Stomach slightly distended. Duodenum not distended.

Experiment 5.—Bitch. Weight 9.8 kg. Fed last time forty-eight hours before operation. Repetition of Experiment 3. Postoperative course the same. Lived one hundred hours. Autopsy. No intestinal leakage. No peritonitis. No distention of stomach or duodenum.

Experiment 6.—Bitch. Weight 10.85 kg. Food withheld for seventy-two hours. Repetition of Experiment 3, section being 12 cm. below pylorus. Postoperative course the same. Temperature varied from 36.6 to 39 C. Lived for fifty-five hours. Autopsy. Same findings as those given above.

Experiment 7.—Dog. Weight 19.7 kg. Fed last time forty-eight hours before operation. Same operation 16 cm. below pylorus. Some peritoneal soiling with intestinal contents. Postoperative course same as others, except more acute. Temperature as high as 39.9 C. Lived only thirty-six hours. Autopsy yielded same findings as others.

Experiment 8.—Dog. Medium weight. Fed six hours before operation. Same operation 12 cm. below pylorus. Postoperative course the same. Temperature 39 C. Lived one hundred and eighteen hours. Autopsy. Same findings and in addition there were noted three superficial areas in the duodenum which resembled ulcers.

Experiment 9.—Leakage of intestinal contents at closed end of proximal gut.

Experiment 10.—Same.

Experiment 11.—Dog. Weight 5.3 kg. Fed twenty-six hours before operation. Same operation 33 cm. below pylorus. Lived only ten to fourteen hours. Autopsy. No leakage. No peritonitis. Stomach was not distended. Mucosa showed small punctuate hemorrhages. Intestine proximal to section and for 80 cm. distal to it was much congested and showed hemorrhagic areas in it. We are unable to explain these last post-mortem findings as being the result of the operation. Our belief, however, is that the early death resulted because of them.

Experiment 12.—Bitch. Weight 9.2 kg. Fed twenty-six hours before operation. Same operation 36 cm. below pylorus. Postoperative course as above. Lived eighty-two hours. Autopsy. Same findings as in other cases.

Experiment 13.—Dog. Weight 8.2 kg. Fed twenty-six hours before operation. Bowel sectioned 36 cm. below pylorus and ends inverted. Symptoms same as others. Temperature 35.5 C. Pulse 180 after twenty-four hours. Lived thirty-eight hours. Autopsy. No peritonitis. Ends of bowel tight. At distal closure an intussusception 14 cm. long had taken place and the intestinal wall was much damaged. This, we believe, contributed to an early death.

Experiment 14.—Young dog. Weight 5.75 kg. Fed seven hours before operation. Bowel sectioned and ends inverted 31 cm. below pylorus. Never fully recovered from operation and died in twelve hours. Autopsy. No peritonitis. Closed ends tight.

Experiment 15.—Dog. Weight 10.5 kg. Fed forty-eight hours before operation. Bowel sectioned and ends closed 48 cm. below pylorus. Postoperative symptoms same as in other dogs. Lived thirty-two hours. Autopsy. No peritonitis. Closed ends tight; 10 cm. intussusception of distal end in gut, with much damage of gut wall. Proximal intestinal mucosa showed much congestion and many punctate hemorrhages.

These animals were operated on in a practically identical manner at varying periods after eating, and none was fed anything after operation. The one which lived the longest, one hundred and sixty hours, was fed twenty hours before operation, and the one that died in ten hours was fed the last time twenty-seven hours before operation. One dog which ate a full meal only six hours before operation lived one hundred and sixteen hours, while one that had fasted for seventy-two hours lived fifty-five hours after operation. The dogs had all the water they would take, both before and after the operation.

There is seen to be a complete lack of correspondence between the state of digestion at the time the obstruction is produced on the one hand, and the severity of the symptoms and length of life afterward. The same thing was noted in all subsequent experiments. It seems, therefore, reasonably certain that alterations of food residues in the tract above the obstruction has little to do with causing death.

The condition of the dogs after operation can be very briefly summarized. They showed a remarkable absence of active symptoms. Recovery from operation was usually prompt and complete, and on the next day they seemed well, but less lively than before. There was a slight rise in temperature Water was drunk freely, and promptly vomited, washing out bile and mucus. Emaciation was marked. After a varying time the animal began to grow weak, but there was a lack of many of the symptoms we are accustomed to see in the human subject. Death seemed to result from general weakness and prostration. There was no abdominal distention, and no sign that cramps or colic were present.

An autopsy was done in every case, and in none was there any gross alteration in the organs that accounted for death. The peritoneum was not inflamed. The stomach and the intestine above the section were sometimes but not always markedly distended. They usually contained only a very small amount of bile and mucus. The mucosa showed a severe congestion. In one or two cases there was a superficial ulceration in the intestinal mucosa. We were struck with the fact that the most severe changes of this character were present in the dogs living the shortest time. We failed, however, to give this observation its full value at that time. The gall-bladder was not distended. The kidneys and liver showed congestion, and the former evidence of degeneration.

From these cases it was determined that animals with a high obstruction might live from five to seven days; that the length of life was not dependent on the presence of food residue in the tract above the obstruction, and that autopsy gave no gross evidence of the cause of death. A complete microscopic study of these cases was not made. Where sections were examined, however, the same lesions were found in the intestinal mucosa, the kidney and the liver, as those to be described in the second group of cases.

We next turned our attention to the production of an obstruction which should not be complicated by any operative damage to the intestinal wall. This was considered advisable because there seemed to be a direct relation between the severity of this damage on the one hand, and the severity of the symptoms and the early death of the dogs on the other.

A special clamp was devised which proved to be efficient in causing a complete obstruction, without opening the intestine or damaging the blood-supply. The clamp consisted of two rubber-covered aluminum plates, about 1 cm. in width and 4 cm. long. Over each end a second covering of rubber tubing was placed. One plate was then passed through a slit in the mesentery, with the bowel passing over it. The second plate was placed across the bowel at this point, and the two plates bound together near their ends. The interval left between them because of the rubber coverings over the ends allowed sufficient room for the intestine, tightly compressed, but not strangulated, to pass through. By bending the plates in or out the degree of obstruction was accurately regulated. We found by experience that the proper degree was obtained when the thin handle of a scalpel could just be passed within the bite of the plates, but not through it.

EXPERIMENTS WITH CLAMP OBSTRUCTION

EXPERIMENT 19.—Male. Weight 13.5 kg. He had been in laboratory seventy-two hours without feeding, and had been given only sterile water to drink. This was done with the idea of getting the stomach and upper intestine as nearly free from bacteria as possible. Cushing and Livingood[15] have shown that the number present can be reduced very markedly in this way. The clamp was placed 18 cm. below the pylorus. The dog remained in excellent condition for five days following the operation. The temperature ranged from 37.5 to 38.5 C. and the pulse from 132 to 150. He drank freely of sterile water, which he vomited soon afterward, washing out bile and mucus with it. He passed small quantities of urine, which contained traces of bile and albumin. During this period he lost 1.8 kg. He showed no active symptoms of the disease, and was in no apparent pain. The abdomen was not tender to palpation, nor was it distended. At operation the circumference of the abdomen was 47 cm. and on the fifth day only 43 cm. After the fifth day he began to show marked weakness and a more rapid loss of weight. The pulse and temperature remained about the same, and no new active symptoms developed. On the seventh day he was markedly weak and walked with difficulty. Emaciation was marked, there having been a loss equal to 19 per cent. of his body weight. He was killed with chloroform one hundred and seventy-two hours after the operation and the autopsy, with bacterial examination, immediately done.

The obstruction was tested under water-pressure, and was found complete, no water passing through the clamped point. Coils of intestine and omentum were matted around the clamp. When these were separated a small local abscess of green odorless pus was opend. The peritoneal coat of the intestine, at this point, was eroded by pressure, but no serious damage was done to the rest of the wall. The general peritoneal cavity was entirely free from evidence of inflammation. The liver and kidneys showed a marked congestion. There was a marked dilatation of the stomach and upper intestinal segment, and both contained water with bile and mucus. Their mucosae were markedly congested.

Microscopical Examination.—The intestine proximal to the clamp shows intense congestion and considerable exudative inflammation of the subserous tissue. The submucosa shows hemorrhagic and leukocytic infiltration. There is an acute hyperplasia of the lymph follicles. Distal to the clamp the intestine is normal. The kidneys show intense capillary congestion, especially of the glomeruli. The epithelium is not well preserved.

The spleen shows congestion.

The pancreas is normal.

The liver sections were unsatisfactory.

The cultures from the abscess around the clamp showed a pure culture of a Gram-negative bacillus, having the characteristics of colon bacillus. Cultures taken from the inside of the intestine, just above the clamp, showed the same bacterial growth, and in addition, a Gram-positive coccus. Our effort to sterilize the upper bowel was not successful, and the local abscess probably resulted from the passage of organisms outward through the intestinal wall, where the peritoneal coat was damaged by the clamp pressure. Other organs were sterile (see table).

EXPERIMENT 20.—Dog. Weight 9.5 kg. No food for one hundred hours. Sterile water during this time. Repetition of Experiment 19. Postoperative symptoms the same. Lived ninety hours. Autopsy (five hours post mortem, during which time the body was on ice) showed no peritonitis. Obstruction complete. Stomach a little dilated. Bowel above clamp twice the normal size. In the intestine, distal to the clamp, were seen many hemorrhagic points.

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15. Cushing and Livingood: Johns Hopkins Hosp. Rep., 1900, ix, 543.

Microscopic Examination.—Intestine proximal to clamp shows fibrinous peritonitis, marked congestion of all coats, and exfoliation of lining mucosal cells. Stomach normal.

Liver: Congestion. Moderate granular and fatty degeneration.

Kidney: Moderate congestion. Tubules show granular coagulum. Cells swollen and show marked granular degeneration. Some cells show partial necrosis.

Cultures from femoral blood, peritoneum and liver show neither aerobic nor anaerobic growth.

Experiment 21.—Puppy. Weight 8 kg. Fed four hours before operation. Clamp applied 16 cm. below pylorus. The stomach contained food and the lymphatics and vessels were distended from full digestion. The postoperative course was the same as in the others. Pulse, 190. Temperature, 39 C. He died fifty-eight hours after operation. Autopsy, eight hours post mortem, the body being on ice. No peritonitis. Moderate distention stomach and duodenum. Few drops of purulent-looking fluid around clamp, buried in adhesions. The obstruction was complete. The gastric and intestinal mucosa, proximal to the clamp, showed very little change. Distal to the clamp there were areas which resembled submucous hemorrhages in the intestinal wall. The other abdominal organs appeared normal.

Microscopic Examination.—Proximal intestine not examined. Distal intestinal mucosa shows hyperplasia of lymph follicle, but no hemorrhages.

Liver: Marked congestion.

Kidney: Congested. Tubule cells swollen, and in places intensely degenerated. Apparent necrosis present in some foci of the tubules.

Spleen and pancreas much congested.

Bacteriology.—Cultures from femoral blood, peritoneum and liver all sterile, both aerobic and anaerobic, with exception of one colony on one peritoneal aerobic slant agar tube. This showed pure growth of a Gram-positive coccus and probably was an air contamination, one of the three found in the whole series.

Experiment 22.—Bitch. Weight 10.25 kg. Fed eighteen hours before operation. Clamp applied 12 cm. below pylorus. This animal was killed on the twenty-first day, up to which time she had showed no symptoms of suffering or of disease, except for loss of weight to 7.4 kg. During this time she had eaten nothing. She drank water freely, however, for the first three days. After this she received 150 to 250 c.c. of normal saline solution subcutaneously, and then she refused water to drink. She only occasionally vomited. The temperature ranged between 37 and 38 C. The pulse for the first four days was about 130. It then became slower and during the last two weeks was between 70 and 100. Urine was passed freely and contained bile and albumin in small quantities. Several blood-cell counts were made during the later days of the experiment and the red cells numbered 5,240,000 and 7,000,000, nearly all counts being slightly over 5,000,000. Killed with ether on the twenty-first day while still in good health. Autopsy. No peritonitis. Clamp allowed minimal drainage into intestine below (compare Experiment 27). Stomach and duodenum were somewhat dilated and the intestine distal to clamp was contracted, showing very little flow into it. It contained bile, however, and under pressure water was forced through the clamp into the bowel below. The mucosa of intestine and stomach appeared normal. The kidneys and liver showed congestion.

Microscopic Examination.—Stomach and intestine not examined.

Kidneys: Tubules filled with granular coagulum. Cells show swelling and granular degeneration.

Liver: Intensely congested.

Spleen: Congested.

Pancreas: Normal.

Bacteriology.—Neither aerobic nor anaerobic growth on tubes from femoral blood, liver or spleen.

Experiment 23.—Dog. Weight 11 kg. Clamp applied 20 cm. below pylorus. He was killed on the tenth day. His symptoms were the same as in cases above. He received saline subcutaneously with apparent benefit. Pulse, 132 to 150. Temperature 37.9 to 39.2 C. Weight at death 8.5 kg. Urine contained albumin and bile. An extensive noma developed on face which accounted for high temperature. Autopsy immediately after death by cyanid. Obstruction complete. Stomach and proximal intestine much dilated. They contained about 300 c.c. of bile, mucus and water. Distal intestine collapsed. The specimen was preserved intact so the mucosa was not seen. No peritonitis. Liver and kidneys much congested. The latter showed acute degeneration, the markings being indistinct and the papillae pale.

Microscopic Examination.—Kidneys showed granular degeneration, in places very marked.

Liver: Intensely congested. Considerable fatty and granular degeneration.

Spleen and pancreas show congestion.

Bacteriology.—Aerobic and anaerobic cultures from femoral blood and liver were all without growth.

Experiment 24.—Small bitch. Weight 6 kg. Fed seventy-two hours before operation. Clamp applied 16 cm. below pylorus. Lived 205 hours—a little less than nine days—with symptoms as in other cases. Pulse, 120 to 180. Temperature average, 39 C. Received saline injections throughout. Red blood-cells increased from 5,000,000 before operation to 6,720,000 on eighth day, showing some loss of water. Weight 4.9 kg. Died during night. Autopsy at 10 in morning. Obstruction complete as tested by absence of bile in distal intestine, although under pressure water could be forced beyond the clamp. No peritonitis. Around the clamp in a mass of omentum there was a collection of dirty yellowish fluid. The intestinal wall showed some damage within the bite of the clamp (see microscopic examination). The stomach and proximal intestine were moderately dilated, and contained a small amount of bile and mucus. The mucous membrane of the whole tract appeared normal to gross examination, as did the kidneys and liver.

Microscopic examination.—The intestine within the clamp showed an advanced purulent peritonitis, destroying longitudinal muscular coat. Congestion of mucosa. Exfoliation of epithelium.

Kidney: Congested. Tubules filled with granular coagulum. Cells swollen and show marked granular degeneration; in places approaching necrosis.

Liver: Section lost.

Pancreas: Marked congestion.

Bacteriology.—Aerobic and anaerobic cultures from femoral blood, peritoneum and liver showed no growth. A Gram-positive coccus was obtained in pure culture from the abscess around the clamp in all tubes both aerobic and anaerobic. This was undoubtedly an infection passing through the intestinal wall where the clamp damaged it, since the same organism was isolated from the intestine.

Experiment 25.—Dog. Weight 6 kg. Fed twenty-seven hours before operation. Clamp applied 16 cm. below the pylorus. He took ether badly and made a poor recovery. He was not given the hypodermoclysis of normal saline solution. Condition seemed good the next day. Died that night. Autopsy not done till day following, about thirty hours post mortem. Obstruction complete under water-pressure. No peritonitis. Stomach and proximal intestine somewhat distended. Distal gut collapsed. Mucosa of stomach and proximal gut markedly congested. Liver, spleen, pancreas and kidneys show congestion.

Microscopic Examination.—Stomach congested. Proximal intestinal mucosa shows intense congestion. Marked round-cell infiltration of tips of villi and exfoliation of cells.

Liver: Intense congestion. Considerable fatty and granular degeneration.

Kidney: Not examined.

No bacteriological examinations made because of delayed autopsy.

Experiment 26.—Bitch. Weight 7.2 kg. Exact duplicate in every way of Experiment 25, except that she received the saline injections daily, the first one of 150 c.c. being given at the close of the operation. She lived ten days, and showed the same symptoms as did other dogs described. Killed with ether and autopsied immediately. Obstruction complete against a column of water 90 cm. high. No peritonitis. The stomach and proximal intestine were dilated to about three times normal. The mucosa of stomach and proximal intestine were congested. The liver, kidneys and spleen were congested.

Microscopic Examination.—Proximal intestinal mucosa shows intense congestion and exfoliation of living cells.

Kidney: Shows congestion. Tubules contain coagulum and occasional blood-cells and show granular degeneration, in places very marked.

Liver shows intense congestion, atrophy of liver cords about distended capillaries and moderate granular degeneration.

Spleen shows much hypertrophy of the follicles.

Pancreas normal.

Cultures from femoral blood, spleen, liver and peritoneum were taken. These were all without growth after four days, under both aerobic and anaerobic conditions, except one aerobic tube (four were taken) from the liver. This showed one colony of Gram-positive cocci growing well to one side of the stroke of the loop.

Experiment 27.—Bitch. Weight 11.5 kg. Fed twenty-eight hours before operation. Clamp applied about 15 cm. below the pylorus. Lived twenty-four days with only moderate development of symptoms during first week. Then behaved like a normal dog. Reoperated on July 20. The clamp was not sufficiently tight to make a complete obstruction (compare with Experiment 22). It was tightened and the next day it had cut its way through the intestinal wall and the dog died of a peritonitis.

Experiment 28.—Dog. Weight 6.5 kg. Fed twenty-eight hours before operation. Clamp applied 11 cm. below pylorus. Postoperative course as in other cases. Died in fifty-six hours and body immediately placed on ice. Autopsy ten hours later. Obstruction complete. No peritonitis. Local infection around the clamp. Stomach and proximal intestine only slightly distended and contained a small amount of bile-stained fluid. The distal intestine was totally empty. Two superficial ulcers were seen in the mucosa of proximal intestine. The liver, kidneys, spleen and pancreas appeared normal.

Microscopic Examination.—Intestine not examined.

Kidney: Tubules swollen and show granular degeneration, very marked in places.

Liver: Intensely congested.

Bacteriology.—Cultures from the femoral blood, the peritoneum, the liver, the spleen and the local collection of fluid around the clamp all were without growth under aerobic and anaerobic conditions.

Experiment 29.—Dog. Weight 8 kg. Fed thirty hours before operation. Clamp applied 11.5 cm. below pylorus. Postoperative course same as in other cases. Received about one-fortieth of body-weight of normal saline subcutaneously daily. He remained in excellent condition for eight days, during which time he lost a little over 2 kg. in weight. He drank water each day, which was always vomited. Pulse from 130 to 174. Temperature, 38.5 to 40 C. On the ninth day he was etherized and the abdomen opened. The obstruction was complete. The stomach and proximal intestine were much distended and filled with a greenish fluid of the thickness of pea soup. There was no peritonitis. The splanchnic vessels were not much dilated, except those above the occlusion. The spleen was not enlarged. The liver and kidneys did not show much congestion. Sections were taken from the stomach, duodenum, distal intestine, liver, spleen and kidney while the dog was still under ether, after which he was killed.

Microscopic Examination.—The stomach is normal.

The proximal intestine shows marked congestion and an edema in the submucosa. The lesions here were not advanced, because the specimens were taken some hours before the animal would have died from the disease. The distal intestine is normal.

The liver is congested. The cells show granular degeneration and areas of necrosis are present.

The kidney is congested. Tubules contain granular coagula. The cells show granular degeneration.

The preceding series includes experiments on eleven animals which may be summarized. In two a complete obstruction was not obtained because the clamp was not sufficiently tight. The two animals were killed after twenty-one and twenty-four days, respectively, while each was in good condition. They had lost considerable weight, and one of them was weak, but otherwise they acted like normal dogs.

The remaining nine dogs all showed a similar condition while living, and autopsy yielded the same findings in the organs. In some dogs, particularly those which lived the longest, the dilatation of the stomach and the duodenum was very marked.

Four dogs in this series were given sterile water by mouth only, and this they promptly vomited. They were, therefore, practically getting neither nourishment nor water, for if what they drank was not all vomited, very little absorption could take place from the stomach and duodenum. Beginning with the fourth dog, each dog received from 150 to 300 c.c. sterile normal saline solution, subcutaneously, per day. This was absorbed. In one case this was not given till the third day. This animal had then begun to act sick, but showed a marked improvement after the administration of the hypodermoclysis. In general, the dogs which received this saline lived longer than the others. They sometimes drank sterile water in addition, but this they always vomited in a very short time. In many cases they refused to drink more than a few cubic centimeters. The three dogs which lived the longest were all given the saline subcutaneously, and there seems no doubt that this procedure was very beneficial.

We attempted, by a count of the red blood-cells, to determine whether the dogs not receiving it suffered from dehydration, with a consequent increase in the number of red cells per cubic centimeter. There was not a sufficient variation from the normal to throw any light on this point, the number ranging around 6,000,000 both before and after the saline injections. The longest postoperative life was ten days (two dogs) ; a third dog lived just under nine days; the shortest period was thirty-six hours in a small fox terrier which never completely recovered from the operation. The average length of life was one hundred and thirty-nine hours in this series, as against sixty-seven hours in the series in which the obstruction was produced by sectioning the intestine and inverting the ends. It was only in this series that the saline injections were used.

It was, moreover, remarked that the second series, in which no damage to the intestinal wall was produced, was much nearer the normal throughout the experiment than was the first series, in which the intestine was sectioned. So far as we know, no other investigator has paid the same attention to producing an obstruction without any damage to the intestinal wall. There is evidence that the method is of advantage in excluding the complications which may arise from such damage. Clinically, we know that when a strangulation, however limited in extent, is superimposed on an obstruction, the course of the disease becomes much more acute. Medowoy,[16] Kocher[17] and others emphasize this point.

Murphy and Vincent,[12] in their experiments, worked particularly on this phase of the question. In a simple obstruction in cats they found the intestinal wall very little damaged in four to six hours. When, however, the circulation was disturbed, particularly a venous stasis produced, a very severe change was present at this time. They conclude that "interference with the circulation of the obstructed intestine is the vital factor in the production of the symptoms of ileus."

When the intestine is sectioned, and the proximal end sufficiently inverted to prevent the stomach and duodenal contents being forced through it, a local strangulation takes place. At autopsy there was always found in these cases a local damage to the intestinal wall at the inverted point, small in extent, to be sure, but nevertheless sufficient to be the possible site of the absorption of a considerable amount of poison. Often, too, a very considerable intussusception of the invaginated stump was present. This mechanical damage, of course, is not an essential in producing death, because it was not present in the second series, in which the animals died. We feel, however, that it has an important bearing on the problem, as we shall later more fully explain.

We desire to call particular attention to the microscopic findings in these cases. The intestinal mucosa, proximal to the obstruction, shows a marked congestion. Marked round-celled infiltration is present, and exfoliation of the lining cells. Hemorrhages are often seen. There is present an acute hyperplasia of the lymph follicles. The submucosa is edematous. Distal to the clamp there is no change, or only a very slight change, from the normal. The gastric mucosa shows only a congestion. The kidneys are markedly congested. The tubules contain granular coagula. The tubule cells are swollen and the seat of granular degeneration; not infrequently necrotic areas are seen.

The liver is congested and the cells show granular and fatty degeneration. Necrotic areas may be present.

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[16] Medowoy: Deutsch. Ztschr. f. Chir., 1910, cv, 1.

[17] Kocher: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1898-99, iv, No. 2, p. 195.

The spleen shows marked congestion, and some hyperplasia of the lymph follicles.

The pancreas shows only congestion.

The changes in the intestinal mucosa are worthy of careful study. They may result from two causative factors. The marked distention and stretching of the intestinal wall may produce a circulatory disturbance or possibly an actual trauma to the mucosa. The stagnated secretions may be sufficiently irritating to damage the mucosal cells chemically. In either case there would develop a condition of lessened resistance, and the intestinal bacteria would be free to attack the mucosa and bring about the changes seen. This having occurred, the changes in the other organs may be conceived as having been caused by the entrance into the blood of poisonous materials which were produced by this bacterial activity. Sufficient evidence that such an explanation is correct is found in the fact, already pointed out, that there is an apparent parallel between the extent of the changes in the mucosa and the severity of the symptoms.

The evil effects of hyperdistention to the intestinal circulation has been experimentally shown by Van Zwalenburg.[18] By means of illumination in the intestinal lumen he watched the circulation when different degrees of pressure were exerted inside the bowel. At a pressure of 30 mm. mercury it was noted that some capillary streams were arrested, while at 60 mm. small veins became blocked. Above this the circulation showed increasing disturbance. If a continuous pressure of from 80 to 90 mm. were continued for an hour, the apparent number of veins seen on the serous surface was greatly increased. Their caliber was also greater than normal. This observation would seem to indicate that the effect of the long-continued distention in a blocked bowel must seriously damage the integrity of the mucosal circulation and lead to the lesions observed in our experiments and recorded above.

The influence of the stagnated secretions above the obstruction may be considered as important in giving rise to poisonous materials which could enter the circulation through the damaged intestinal wall. In order to study this phase of the question, we turned our attention to an elimination of the bile, pancreatic and duodenal secretions as a source of the poisons. To this end, in five dogs the following operation was done: The pylorus was divided and the two cut ends closed by inversion. The intestine was divided just distal to the duodenum, and the proximal end implanted in the jejunum about 30 cm. lower down. The distal end was implanted into the stomach. By this means the stomach emptied into the intestine just below the duodenum, and the bile, pancreatic and duodenal secretions passed into the jejunum about 30 cm. distal to this. Our intention was to cause an obstruction with the clamp, just orally to the new duodenal outlet when the animals should have recovered from the anastomoses, thus having an obstruction of the stomach and about 30 cm. of the intestine but not of the duct-bearing portion of the tract. For a few days following the operation these dogs did well, fully regained their appetites and seemed to be in good health. After about a week, however, they began to act sick. They did not eat well, and sometimes vomited. They lost weight rapidly. Some of them developed diarrhea with bloody-appearing stools. Four of them died in about four weeks with evidence of malnutrition. The autopsy showed, in two of these, that a very extensive damage to the intestine between the stomach and duodenal anastomosis was present. Ulcers were seen which were about to perforate. The stomach and this part of the intestine contained partially digested blood.

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[18] Van Zwalenburg: Ann. Surg., November, 1907, xlvi, 780.

The fifth dog seemed to be in fair condition after two weeks, and on the nineteenth day the abdomen was opened under ether anesthesia. The anastomoses were satisfactory and no evidence of ulceration was present from the peritoneal surface. The occlusion clamp was applied just above the anastomosis of the duodenum with the jejunum. The following day the dog was in good condition; he had not vomited. He was given saline subcutaneously. He died during that night and autopsy was done in the morning. The anastomoses were satisfactory. A general peritonitis was present from a perforation within the bite of the clamp. The stomach and intestine anastomosed to it were distended with a dirty brownish fluid. When they were opened the gastric mucosa was seen to be much congested; the mucosa of the jejunal segment was markedly congested and contained many hemorrhagic areas. The intestine below the duodenal anastomosis was entirely normal in appearance. The effort to produce an obstruction in which the duodenal contents should not be stagnated had not been successful. But the symptoms developing in these dogs and the findings in the intestinal mucosa added emphasis to the relations existing between these two factors. In many ways these dogs behaved like the ones with an obstruction, the symptoms and the course of the disease being, however, much less acute. The microscopic examination of the intestinal mucosa, the kidneys and the liver, showed, too, the same lesions as found in the simple obstruction.

The fact that such damage to the intestinal wall, in so far as it occurs in intestinal obstruction, is the cause of serious symptoms, and, if extensive enough, may even cause death, seemed to be well demonstrated. That it is the sole factor, however, was not proved, and as stated above, our attention had been arrested by the benefit derived from the administration of salt solution under the skin. It was conceivable that this benefit arose from diluting and eliminating the poisons absorbed through the damaged intestine. Such a supposition, however, had no support in any work done, and accordingly a more detailed study of this question was undertaken, and for this purpose Dr. Benedict, of the department of chemistry, kindly offered to make some studies in metabolism for us. To him we are indebted for a most important discovery which, we believe, throws much light on the question under consideration, if it does not completely solve the problem of the cause of death from uncomplicated intestinal obstruction.

EXPERIMENT 1.—The first dog under his observation was a female in good condition, weighing 12.1 kg. The clamp was applied under ether narcosis on the lower part of the duodenum, March 4, 1912. Table 3 gives the results found during the three and a half days that she lived.

TABLE 3.—RESULTS OBTAINED AFTER CONSTRICTION OF THE LOWER PART OF THE DUODENUM FOR THREE AND ONE-HALF DAYS

Date	Weight, kg	Urine, c.c.	Vomitus, c.c.	Combined Fluid Output, c.c.	Total Nitrogen, gm.	Remarks
3/4/12	12.10	..	....	....	....	Clamp applied to lower duodenum.
3/5/12	11.28	26	720	746	....	Received 100 c.c. of a 0.9 per cent. saline solution.
3/6/12	10.36	15	500	315	10.334	Received 100 c.c. of a 0.9 per cent. saline solution.
3/7/12	9.86	86	510	596	....	Received 100 c.c. of a 0.9 per cent. saline solution.
3/8/12	....	..	....	....	....	Died.
Totals,	....	127	1,730	1,857	....	

From these figures it is seen that she lost 2.2 kg. in weight. Her output of fluids, including the urine and vomitus, but not counting the water of expiration, was 1,857 c.c., to offset which she had only received 300 c.c. subcutaneously. The total nitrogen output in two days was 10.34 gm., which equals, approximately, 0.5 gm. per kilo per day, which is two or three times the normal output. A sample volume of urine of 127 c.c. contained 3.574 gm. albumin. The creatin excreted in this equaled 0.638 gm., which was more than double the amount of creatinin.

It was obvious from these figures that a very severe grade of tissue disintegration was taking place, and that a water loss averaging about 5 per cent. of the body weight was suffered each day. It at once became apparent that the amounts of water we had been giving were entirely inadequate to replace this great loss, and that probably death was much hastened by such a loss.

Accordingly, we made a study of three dogs in which the daily output was measured, and a quantity of normal saline about 100 c.c. in excess of this was injected under the skin. These dogs with the clamp applied on the lower duodenum were kept alive in this way for three weeks (one for twenty-six days), and during this time they remained in good condition. They were then etherized a second time, and the abdomen opened to see if the obstruction were complete. In every case it was found to be so. The stomach and the duodenum above the clamp were excessively dilated, and their contents could not be forced through the clamp into the intestine below, which was found empty and much contracted. By varying the amount of water injected, we could accurately control the condition of the dogs. The complete study of one of the experiments is shown below.

TABLE 4.—RESULTS OBTAINED WITH CLAMP ON THE DUODENUM FOR THREE WEEKS AND INJECTIONS OF SODIUM CHLORID

Date	Weight, kg.	Urine, c.c.	Vomitus, c.c.	Combined Fluid Output, c.c.	Injection 0.9% NaCl. Sol., c.c.	Remarks
3/13/12	11.3	....	....	....	....	Clamp applied to lower duodenum.
3/14/12	....	120	420	540	250	
3/15/12	....	175	—	175	200	
3/16/12	....	160	600	760	200	
3/17/12	10.46	170	—	170	200	
3/18/12	10.84	135	—	135	500	
3/19/12	....	†	†	...	150	
3/20/12	....	130	850*	980	250	
3/21/12	9.64	130	—	130	550	
3/22/12	10.24	100	550*	650	850	
3/23/12	....	80	800*	880	500	
3/24/12	10.24	...	...	...	600	
3/25/12	9.68	70	1,180*	1,250	750	
3/26/12	....	†	†	...	800	
3/27/12	....	85	1,160*	1,245	800	
3/28/12	10.00	310	—	310	700	
3/29/12	....	562	150*	712	300	
3/30/12	....	390	—*	390	200	
3/31/12	....	150	200*	350	200	
4/ 1 /12	....	55	80*	135	150	
4/ 2 /12	8.9	55	—*	55	100	Is in excellent condition.
4/ 3 /12	8.3	...	650	650	—	Obstruction found complete. Clamp removed. Recovery.
Total for 21 days.....		2,877	6,640	9,517	8,250	

* Obtained by stomach-tube. † Incomplete. — None.

Experiment 2.—A bitch weighing 11.3 kg. had the clamp applied under ether narcosis, on the lower duodenum, March 13. April 3, twenty-one days later, when in excellent condition, she was again etherized and the abdomen reopened. The obstruction was found to be complete. The clamp was removed and she is still alive. The total vomitus during the twenty-one days was 6,640 c.c. and she received to offset this 8,250 c.c. of saline solution. Much of the vomitus had to be obtained by the stomach-tube, as the stomach became dilated and would not empty itself. She lost 3 kg. in weight. The study of the urine gave most interesting results. During the first week it showed very marked abnormalities. The albumin content was as high as 4.5 gm. per day, and the total nitrogen, exclusive of this, was, on an average, 5 gm. The creatinin-creatin ratio was about 1 to 2 instead of 10 to 1, which is near the normal for a starving dog. The latter ratio was later established. During this week the vomitus was 1,870 c.c. in amount, which was 120 c.c. more than the amount of saline solution administered. The urine equaled 890 c.c., so that there was a loss of water equal to one-tenth of the body-weight. The condition of the animal was only fair during this week. After the seventh day the saline was increased to 550 c.c. daily and maintained there, or higher, for several days. The abnormalities in the urine entirely disappeared, and it became the urine of a dog under normal starvation, except that it contained bile throughout. There was coincident improvement in her condition. Later, on the sixteenth day when vomiting had ceased and the stomach-tube recovered very small amounts, the saline was again decreased to 200 c.c. or less; the dog remained well, and the urine continued normal.

Experiment 3.—A small bitch weighing 5.88 kg. had the clamp applied under ether narcosis to the lower duodenum, April 8, 1912. She received the normal saline solution subcutaneously, every day, the first injection of 300 c.c. being given immediately after the operation. The quantity was repeated on the two following days, and then for sixteen days she received 400 c.c. daily, and for two additional days 300 c.c. each. The total saline administered during the continuance of the experiment for twenty-one days was 7,900 c.c. an average of 376 c.c. per day, which was equal to about 8 per cent. of her average body-weight. During this time the total amount of fluids excreted in the urine and the vomitus was 6,354 c.c. Much of the vomitus had to be excreted by means of the stomach-tube because the stomach became atonic and vomiting ceased even though the organ was full. Her loss in weight was 1.4 kg. Throughout the entire experiment she remained in a condition of apparent perfect health. She was always playful and lively. On the twenty-first day she was etherized and the abdomen was reopened. The clamp was found *in situ* and the obstruction was complete. Four hundred and fifty c.c. of water were put in the stomach through the tube. This readily passed through the pylorus and down the duodenum to the clamp, where it was completely stopped. It was impossible to force any beyond the clamp by direct pressure on the duodenal wall. The clamp was removed and a small perforation, which was completely closed by the rubber covering of the plate and by adhesions, was found in the bite of the clamp. There was no peritonitis.

EXPERIMENT 4.—A bitch weighing 12.2 kg. had the clamp applied under ether narcosis to the lower duodenum, April 19, 1912. During the following six days she received 1,500 c.c. of normal saline solution subcutaneously, and excreted in the form of vomitus and urine 1,020 c.c. On the seventh day she did not vomit, and the stomach-tube recovered nothing. We suspected that the clamp was not tight enough to produce a complete obstruction, and she was accordingly given 500 c.c. of water through the stomach-tube and a quantity of meat which she ate greedily. Following this she again vomited, and in four days put out 2,150 c.c. in which the digested meat was present. The injections were then increased, quantities varying from 700 to 500 c.c. being given daily. The vomiting ceased and a quantity of urine was passed, slightly less than the saline injected, the total for seven days being, saline 4,000 c.c., urine 3,200 c.c. The saline was again decreased, and the urine fell, but no vomiting recurred. She was etherized May 16, twenty-six days after the obstruction, and the abdomen was reopened. The obstruction was found to be complete. The stomach and duodenum were found to be enormously dilated, having a capacity of 1,000 c.c., while the intestine below the clamp was contracted and empty, not showing any trace of bile. No detailed study of the urine was made in this or the preceding case.

It will be noted that in many instances there was no vomiting, but the stomach-tube recovered large quantities. This must be taken into account in determining the amount of saline to be administered, because whether vomited or retained in the stomach, it means a loss to the animal. These three dogs were under identical conditions with the nine previously reported, except that they received amounts of normal saline solution about 100 c.c. in excess of the daily output of vomitus, often reaching 500 to 700 c.c. per day, while the animals in the former series received only 150 or 200 c.c. per day. No dog in the first series lived longer than ten days. All dogs in the later number were alive and in good condition at the end of three weeks, and apparently would have succumbed only to starvation if the experiment had been continued.

In order to be certain that no leakage took place, an obstruction was produced in two dogs by dividing the lower duodenum and closing the ends by inversion. The result was the same as in the dogs having the clamp applied. Care must be taken, however, to minimize the amount of damage done to the intestinal wall in this operation, otherwise the animal is poisoned from this source and may die.

From these results it is plain that the loss of fluid from the organism is the disturbing influence and is the important factor in explaining the symptoms and death following uncomplicated high intestinal obstruction in dogs. Death is caused by the loss of water which the tissues sustain from the excessive amounts vomited, and death can be prevented if this water be replaced by cutaneous injections of normal salt solution.

The source of such enormous amounts of vomitus is a matter of interest. Dr. Benedict's study of the vomitus from the experiment detailed under Table 4 showed it to be strongly acid, and to have a specific gravity of 1.007. The total amount contained 16.72 gm. of chlorin, which, computed as sodium chlorid, equals 27.65 gm. Bile was always present. The low specific gravity indicates that it was largely water. These findings show, as would be expected, that the vomitus is a diluted mixture of bile and gastric secretion. The part played by the pancreas and duodenum is unknown. In all the cases the vomitus was more abundant during the early part of the experiment than it was later, and toward the end it often almost entirely disappeared. The following considerations offer an explanation of this unexpected fact. The dogs were all in good condition when operated on, and presumably the liver and other glands were actively secreting. The products of these glands, bile, pancreatic juice and duodenal secretion, found no outlet beyond the duodenum, and hence were forced back into the stomach. Here they acted as an irritant to the gastric mucosa, and as a result a secretion of gastric juice and an excretion of water took place to the enormous amounts found. As the experiment proceeded the dog gradually developed the condition of a starving animal in which all the alimentary glands become inactive, the bile in particular being very small in amount. The disturbing influence of these retained secretions being absent, the vomiting gradually grows less, and finally almost ceases. The small amount of bile secreted is taken care of in the duodenum and stomach, being either digested or absorbed. That some is absorbed is shown by the fact that the urine contains bile throughout the experiment. The bile alone, however, is not the offending factor, because in cases in which the common bile-duct was tied and an anastomosis made between the gall-bladder and the intestine below the clamp, large amounts of vomitus appeared, though not equaling those above given.

The results of all our work demonstrated, therefore, that there are two important factors concerned in producing the symptoms and causing death in a high intestinal obstruction in dogs.

First, the loss of water from the tissues caused by the excessive drainage into the intestinal lumen followed by vomiting. This factor is entirely under therapeutic control. It can be rendered harmless by the subcutaneous administration of normal saline solution.

Second, the absorption of poisonous materials from the intestinal wall, when, by reason of overdistention and chemical irritation the mucosa is damaged and bacteria set up an active inflammation in it, and possibly the other intestinal coats. This factor is not appreciably influenced by the administration of the salt solution.

REVIEW OF THE WORK OF WHIPPLE, STONE AND BERNHEIM

We have referred above to the work done by Whipple, Stone and Bernheim, which appeared[3] after preliminary reports of our work had been published,[19, 20] setting forth the conclusions just given. As their conclusions differ in important particulars from ours, it seems advisable to compare the two, and if possible reconcile the facts as a basis for the correct conclusion. In doing this we shall quote freely from an article already published,[21] in which this phase of the subject was treated.

Whipple, Stone and Bernheim,[22] studied the question by producing a closed loop of the duodenum, beginning just below the pancreatic ducts and ending beyond the suspensory ligament. This portion was isolated from the remainder of the intestinal tract by tying a heavy ligature tightly at these two points, and burying it under an inverted layer of the peritoneum. A gastro-enterostomy was then done. Dogs so treated died in from thirty-six to seventy-two hours. The authors inferred from this that there developed in the closed loop a poisonous material, the absorption of which caused death. Since the closed loop contained neither gastric secretion, bile nor pancreatic juice, the conclusion seemed inevitable that some alteration in the loop function was responsible for death.

A series of careful and well-controlled eperiments was then undertaken to study the nature, and if possible, to determine the source of any poison. The method employed was to produce the isolated loop, collect the contents, sterilize them by heating to 60 C., filtering them, and then, after autolysis, to inject them into a healthy dog, intravenously, subcutaneously or peritoneally. It was demonstrated in this way that dogs so injected died promptly. Further, the authors were unable to isolate any poisonous material from the normal intestine by any method of treatment; and if the mucosa of the loop were first destroyed by a

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[19] Hartwell and Hoguet: Am. Jour. Med. Sc., 1912, cxliii, 357.

[20] Hartwell and Hoguet: Experimental Intestinal Obstruction in Dogs, with Especial Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, Jour. Am. Med. Assn., 1912, lix, 82.

[21] Hantwell, John A.: Jour. Exper. Med., 1913, xviii, No. 2, p. 139.

[22] Whipple, Stone and Bernheim: Jour. Exper. Med., 1913, xvii, 286.

fluorid, no poisons appeared. Lastly, some dogs died within a few days when the loop was drained externally, there being, according to the authors, an absorption directly from the mucosa, and not from the lumen.

The authors summarize, in part, as follows:

> There seems, therefore, no escape from the conclusion that a poisonous substance is formed in this closed duodenal loop which is absorbed from it and causes intoxication and death. Injection of this toxic substance into a normal dog gives intoxication and a reaction more intense than, but similar to, that developing in a closed loop dog (p. 306).
>
> The mucosa of closed or drained duodenal loops contains a toxic substance quite similar to the toxic material found in the lumen of the closed loops.
>
> Normal intestinal mucosa contains no toxic substance nor can it neutralize *in vitro* the toxic substance produced in the closed loops. Our experiments show that formation and absorption of a toxic substance may proceed in a loop whose blood-supply has in no way been disturbed, and whose mucosa is quite intact both in gross and microscopically (p. 323).

The authors apply their findings to the condition of simple intestinal obstruction, and state it as their belief that "the toxic material concerned is the same in both instances" (p. 321). They add: "Our experiments indicate that intoxication is the primary effect, and the loss of body fluids a secondary one, rather than the reverse, as is claimed by Hartwell and Hoguet."[20] In substance, they claim to have proved that a closed loop of intestine, without undergoing any morphological change, produces a toxic substance which is absorbed and causes death. Moreover, they infer that a similar condition exists in simple intestinal obstruction, and that here also death results from the absorption of this same poison.

We fail to find any evidence in their experiments, as published, to justify these claims. On the contrary, we find that the protocols definitely show a damage to the intestinal wall, and that the toxic substance they are dealing with arises from this source. In the absence of this damage no toxemia is present except that produced by the loss of water in the vomitus. We submit the following review of their protocols in support of this view:

Dog S-34.—Moribund in twenty-seven hours. Killed with ether. Autopsy immediately. "The duodenal loop is of enormous size." "Purplish patches show through the transparent serosa." "The contents are blood-stained."

Microscopical Examination.—"In places the wall of the duodenum shows necrosis, hemorrhage and invasion by leukocytes."

Dog S-27.—Died in thirty-two hours.

Autopsy.—"The duodenal loop is contracted and contains a little material. Its walls show a few areas of subserous hemorrhage, about 1 or 2 cm. in diameter. There is obvious necrosis associated with these areas, and through one of them rupture had taken place, with escape of duodenal loop fluid into the peritoneum." No microscopical examination is given.

Dog S-20.—Death in forty-eight hours. One hundred c.c. of fluid are in the loop. "The closed loop mucosa is pinkish and a little swollen, but no ulcers are present." The proximal loop was not tight, and some fluid had probably regurgitated into the stomach.

Dog 56.—Death in fifty-five hours. Remained well for twenty-four hours.

Autopsy.—"The abdominal cavity is clear except for slight granular peritonitis about the loop and area of operation." "The small intestine below the loop contains blood-stained mucus, and its mucosa has a mottled appearance, with large areas of deep red color where the capillary injection is quite marked. The duodenal loop is rather flabby and not greatly distended. It contains about 50 c.c. of a thin, soup-like, faintly blood-tinged fluid. The loop mucosa is quite intact, but of a delicate pinkish tinge." No microscopical examination is given.

Dog S-53.—Death in three days. Seemed well for twenty-four hours.

Autopsy.—The condition of the loop mucosa is not given; it is merely stated that it is pink and intact. No microscopical examination is given.

Commenting on these four experiments the authors say:

> The duodenal loop may show a normal intact mucosa in gross and microscopically, except for a little diffuse injection. Again, it may show necrosis, ulceration and hemorrhage, and the contained fluid may vary correspondingly in characteristics, but it always contains a toxic substance (p. 291).

In only one case, however, is a microscopical examination given, and then marked changes were found, while in the others evidence of change was seen grossly. The length of life seems directly to correspond to the lack of damage found in the mucosa, as demonstrated by the reported findings in Dog S-53, which lived for three days.

The following protocols give the conditions found in the duodenal loop, when the dog is killed at the end of twenty-four to twenty-eight hours. In one case, Dog S-4, the contents were blood-tinged, owing to inversion of the duodenal mucosa.

Dog S-4.—"The mucosa throughout the loop is intact, but slightly swollen and of a pinkish color."

Microscopical Examination.—"The tips of a few of the villi are slightly swollen and contain a few polymorphonuclear leukocytes. The epithelium is normal throughout."

Dog S-2.—In twenty-six hours the duodenal loop contained blood-tinged fluid: in places, on microscopical examination, "it shows some areas of necrosis with hemorrhage and invasion by pus cells, involving mucosa and submucosa."

Dog S-5.—The loop contained blood-tinged fluid.

Microscopical Examination.—"The duodenal loop is quite normal."

In two dogs, S-28 and S-29, the duodenal loop contents were not blood-tinged, and the mucosa, on gross examination, seemed normal, though no microscopical examination is given.

These dogs were all in fair condition when killed, being described as "dull and drowsy," "weak," "pulse strong," "somewhat dull but not very toxic." The incipient damage to the mucosa, as shown in these cases by the blood-tinged fluid and the microscopical examination, explains the cause of their condition. We cannot reconcile a normal mucosa with a blood-tinged content, as reported in Dog S-5.

Dogs S-12 and S-9.—Both dogs were killed after forty-four hours, and were apparently in fair condition, Dog S-9 showing a carotid pressure of 100 to 110 mm. of mercury, with almost normal pulsation. There were no visible changes in the loop mucosa, either on gross examination or microscopically.

Dog S-38.—The dog was killed after forty-eight hours, his condition being "somewhat toxic." "The blood-pressure was practically normal and the pulse regular." "The duodenal loop contains 20 to 30 c.c. of a strawberry-colored thick fluid. The loop shows a diffuse pinkish mucosa, no ecchymoses and no ulcers."

These dogs were killed after from forty-four to forty-eight hours, when in good condition, and no change was found in the mucosa. If the enclosed secretion from the mucosa itself is the active poison, the absorption of which, by the mucosa, causes death, why are the dogs not made more ill? We believe it is because in these individual cases the mucosa was not so severely damaged. If we compare them with Group 1, in which the dogs were allowed to die, and with the group immediately preceding, in which at the end of approximately twenty-four hours the dogs were apparently more toxic, and a definite change in the mucosa was found, we cannot escape the conclusion, from a careful analysis of the cases, that the severity of the toxic symptoms is in direct ratio to the damage done to the mucosa.

In their injection experiments (pp. 301-304) the authors prove beyond question that they have obtained from the contents of the closed loop a substance, which, after sterilization by heat (60 C. for thirty minutes) and filtering through a Gooch or other porcelain filter, is very poisonous, and will cause death in a few hours, if it be injected into the vein, the peritoneum or the subcutis of a dog.

Whipple, Stone and Bernheim find that a similar poison can be extracted from the mucosa (not the loop content) of a non-drained or a drained closed loop, injection of which into dogs produces severe toxic symptoms (pp. 310-311). They argue from this that the substance with which they are dealing is elaborated in the mucosa of the closed loop, and that some unknown force is at work which profoundly alters the activity of the epithelial cells. Yet they emphasize the fact that there is no demonstrable change from the normal. Where do they conceive this toxic substance to arise? They disprove Draper Maury's contention that it is a normal output of the mucosa, which is poisonous unless neutralized with fluids from other portions of the alimentary tract, by showing that duodenal loop fluid, digested with normal intestinal mucosa, loses none of its toxicity (p. 316). With a normally secreting mucous membrane, undergoing no change from the normal, it is difficult to conceive how there is rapidly formed a very toxic material which is directly absorbed from it into the general circulation, with resulting death. It seems inevitable that severe changes take place in the mucosa —they are usually demonstrable—and that the toxic material comes from this alteration in the mucosa. In all cases in which death occurs from the closed loop itself some evidence of damage to the mucosa is described, and the severity of the symptoms runs parallel to the severity of the demonstrable damage.

A careful study, therefore, of the findings of these authors makes us unwilling to accept their conclusion that a poisonous substance is poured out by a normal mucosa, or elaborated and directly absorbed by the normal cells, which substance produces the toxic symptoms in simple high intestinal obstruction. In discussing the fact that dogs with a simple obstruction may be kept alive at will by simply replacing with normal saline solution the fluid lost in the vomitus, Whipple, Stone and Bernheim say that the benefit derived "is due to dilution and elimination of the toxic material by this means, and the development of a gradually increasing immunity which can be shown to appear in dogs after intravenous injection of the toxic substance" (p. 321). Yet they report conclusive experiments showing that their toxic substance neither exists in the blood of a closed loop dog nor remains for two hours in the blood of a dog that has received a lethal dose intravenously (p. 309). It is difficult to comprehend, then, how saline solution given once a day is capable of washing out from the blood a substance which, within two or three hours, is "fixed by the cells or partly destroyed," and which, if not washed out, will inevitably cause death. If this were possible, one ought to find a cure for organic poisons by a hypodermoclysis, and, similarly, the closed-loop dogs ought to be saved by this means.

In commenting on the claim of Hartwell and Hoguet,[20] that this action of salt solution is a strong argument against an essential toxemia, and that the loss of water is the important factor, Whipple and his associates say: "One might argue in the same manner that the appearance of sugar in the urine is the cause of diabetes." The analogy is incorrect. Were it possible to alleviate diabetes by the subcutaneous injections of sugar, to the extent that obstruction may be alleviated by injections of saline solution, the analogy would be acceptable, the loss of sugar being the prime factor in one case, and the loss of water in the other.

Moreover, the most potent argument of Hartwell and Hoguet in this connection—a normal starving metabolism when saline is given, and a completely deranged one when it is withheld, as determined by Benedict —is entirely ignored by Whipple, Stone and Bernheim.

It is our contention that the experiments cited by these authors have no bearing on the subject of *uncomplicated* obstruction. They show, however, that a damaged intestine will produce a substance which is very poisonous if it gain access to the blood. This is exactly the same conclusion we arrived at by a different method of investigation and reasoning.

Still further to test the question, we produced the doubly closed loop in different parts of the bowel on a series of dogs.

The experiments with a doubly occluded loop of intestine, made either by section and inversion of the ends, or by the clamps, need not be detailed because they duplicated in every way the results obtained by Whipple, Stone and Bernheim. It is worthy of note, however, that dogs with the double closure in the middle of the jejunum showed the same symptoms and died in the same way as those with a duodenal doubly closed loop. When the jejunal loop became distended with its secretions, and the mucosal circulation was damaged, the animals became sick and ultimately died. The course, however, was less acute. This proved that death is not due to any specific action of the duodenal mucosa, as Whipple, Stone and Bernheim assume. When, however, a double occlusion is produced in the lower ileum, or the cecal region, the animals are not sick, and they may live an indefinite time. Similar results have been obtained by von Baracz.[23] They are explained by the fact that this part of the intestine secretes very little fluid and consequently there is no distention, no damage to the mucosa, and no absorption of the poisons which higher up result from such a damage.

A series of experiments performed by us with the object of preventing such a damage even in the duodenum gave important results. We believed that if we could minimize the amount of fluids poured out into the duodenal loop and the operative damage to the bowel wall, we could longer retain an intact mucosa, and hence longer delay the fatal outcome. To accomplish this the operation was done in two stages. At the first stage the bowel was sectioned just below the pancreatic duct and the two ends closed by inversion, with as little operative damage as possible. The continuity of the alimentary canal was then reestablished by a lateral anastomosis between the upper duodenal segment and the beginning of the jejunum. In this way there existed a segment of the duodenum below the ducts which was closed at the upper end and drained by continuity directly into the jejunum. The animal was allowed to recover completely from this operation during a period of two weeks. He was then kept without food for four days, and the second stage operation performed. At this time the lower end of the duodenum was sectioned at the site of the entero-enterostomy and the two ends closed, the same care being taken to avoid needless damage to the mucosa in doing this. Thus, there resulted a doubly closed duodenal loop. Following this operation the animals received no food or water by mouth, but were given saline subcutaneously. This was done with the belief that absence of the stimulation from food would materially decrease the secretions in the closed loop, and thereby prevent its overdistention.

In a series of dogs we were able to get a positive result in two in that with a double occlusion of the duodenum without visible damage to the mucosa death did not result as it usually does in the one stage operation with its inevitable damage to the mucosa.

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[23] Von Baracz: Arch. f. klin. Chir., 1899, lviii, 121.

DOG 107.—May 1, 1913: An entero-enterostomy was done between the duodenum just below the pancreatic duct and the first part of the jejunum. The bowel was then sectioned and the ends closed by inversion at the proximal end of the loop of duodenum thus formed. Recovery from this operation was completed by May 3, after which he was regularly fed and seemed to be quite normal.

May 12 to 16: All food withheld but water given freely.

May 16: Abdomen again opened, and the distal end of the duodenal loop was sectioned near the anastomosis and the two ends closed by inversion and suture. Thus there was formed a doubly occluded loop of the whole duodenum, while an entero-enterostomy reestablished the intestinal patency. Following this operation he was moderately sick for four or five days. He vomited somewhat. He was given all the water he would drink and no hypodermoclysis. At the end of a week he seemed entirely normal, ate greedily and had no trouble in digesting food. On the seventeenth day after the second operation, the abdomen was again opened. The duodenal loop was found tightly closed at both ends and practically empty. The mucosa was slightly congested, but otherwise quite normal.

DOG 108.—The same procedure was followed as in the previous case. Twenty-five days after the second operation the abdomen was opened and the loop examined. In this case there had been a reestablishment of the lumen from the distal end of the loop into the intestine. This had been possible because after sectioning the bowel, and inverting the two ends at the second operation, they had been fastened in apposition so as to prevent an intussusception. It is not conceivable that this could have resulted under one week, so that the dog lived during this time in good health with a doubly occluded duodenum.

In the whole series of doubly occluded duodena which we did, there was always a direct relation between the severity of the symptoms and the shortness of postoperative life on the one hand, and the amount of mucosal damage on the other.

The two cases cited above we submit as giving final proof to our contention that there is no fatal poison arising from the duodenum when there is no damage to the mucosa.

LOW OBSTRUCTION

Having demonstrated the causes of death in high intestinal obstruction we next turned our attention to a study of an obstruction lower down. In the following, the obstruction was produced by clamp in lower ileum or at cecum, and treated with small amounts of normal saline solution.

DOG 48.—Weight 13.5 kg. Fed twenty-four hours before operation. Clamp applied just above cecum.

December 12: Vomiting large amount of bile-stained fluid. Given water by mouth and 200 c.c. subcutaneously. Condition good.

December 13: Drank water greedily; 200 c.c. saline subcutaneously. Condition good. Temperature, 40. Pulse, 120. Vomiting somewhat.

December 14: Same.

December 15: Condition not so good. Acts sick. Pulse 145.

December 16: Very sick. Vomitus excessive. Bright red in color. Fecal in character and very foul. Pulse 180.

December 17: Died during night. Lived five and one-half days.

Autopsy.—Obstruction complete. Small abscess around clamp. No peritonitis. Very intense congestion throughout peritoneum. Kidneys and liver intensely congested.

Alimentary Tract: Stomach not distended, but mucosa somewhat congested. Duodenum the same. The entire ileum is greatly distended, wall thin, mucosa intensely congested. In lower part hemorrhagic areas are present, and in spots superficial areas of necrosis exist.

Damage to mucosa caused death.

Dog 50.—Weight 5 kg. Fed few hours before operation. Clamp applied just above cecum.

The postoperative condition exactly parallel to that of Dog 48. Remained in excellent condition for three days; then began to sicken and died after five and one-half days. He received from 150 to 210 c.c. water subcutaneously each day and drank in addition. Vomited every day.

Autopsy.—Obstruction complete. No peritonitis. Same changes found as in Dog 48. The ileum above the clamp was enormously distended and black in color. No actual necrosis seen. Kidneys and liver markedly congested.

Dog 52.—Fed twenty-four hours before operation. Weight 12 kg. Clamp applied just above cecum.

Postoperative behavior as in previous cases, except that he remained well for nine days, after which he grew sick. Received 200 c.c. of saline subcutaneously each day. Vomiting much less than in other cases.

Killed with ether on tenth day while in apparent fair condition.

Autopsy.—Obstruction complete. No pertitonitis. Upper bowel empty. Lower ileum much congested, markedly distended and containing a quantity of foul-smelling liquid, fecal matter. There was a marked peristalsis still present, and the fluid contents of the bowel could be seen continuously forced downward to the site of the obstruction. There was no marked evidence of the damage to the intestinal wall seen in the other cases. The liver showed some congestion, but otherwise the organs appeared normal.[24]

Cultures from the peritoneum, femoral blood, spleen and liver all proved negative, both anaerobically and aerobically.

This type of experiment was done six times, and the results accorded in every way with the three here described. Length of life exactly paralleled the lack of injury to the intestine as it had done in the high obstruction.

In the following low obstruction was treated with excess of saline subcutaneously:

Dog 85.—Clamp applied 62 cm. above the cecum. Normal saline, 400 c.c., was given subcutaneously at the end of the operation. This was repeated the next day, but in spite of it the dog only lived forty-six hours.

Autopsy.—No peritonitis. Obstruction complete. The bowel below the clamp is collapsed and empty. Above the clamp the bowel is dilated all the way to the stomach, being four or five times the normal diameter for a distance of 150 cm. This intestine shows very marked vascular changes throughout this length, as instanced by the presence of deep ecchymoses which involve all the coats except the peritoneal, through which, however, they are readily seen.

These changes are most marked on the convex border of the intestine, the surface at which the circulation would be naturally most disturbed by the excessive distention. There are no actual ulcers or necrotic areas seen in the mucosa.

Microscopical Examination.—The intestinal mucosa in the above areas is practically destroyed. There is edema throughout the entire wall of the bowel.

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[24] The length of life, and the absence of symptoms for such a long period, was due to lack of excessive vomiting and lack of damage to the intestine.

Between all the layers is a beginning purulent exudate with hemorrhages. These changes are probably of microbic origin.

DOG 86.—Clamp applied 40 cm. above the cecum. Dog remained perfectly well for three days. On the fourth day he began to act sick, and on the fifth day was greatly prostrated though still able to walk around the laboratory. During the five days the total output of urine and vomitus was 2,030 c.c., which was replaced by the administration of 2,050 c.c. of normal saline solution. The dog was killed with ether and the autopsy immediately done.

Autopsy.—No peritonitis. The clamp was tight and produced a complete obstruction. The bowel above the clamp was moderately distended for a distance of 50 cm., and shows no gross changes on peritoneal surface, except for congestion immediately above the clamp.

When the bowel is opened there are seen many scattered small areas where the mucosa is much damaged, in places showing a beginning necrosis. The content of the bowel is ordinary fluid fecal material.

Microscopical Examination.—There is an almost complete necrotic destruction of the mucosa at the points mentioned above. The entire thickness of the bowel wall is edematous and shows signs of acute exudative inflammation.

Kidneys: Acute parenchymatous inflammation is present.

Liver: Granular and lipoid degenerative changes are present.

DOG 88.—The clamp was applied 100 cm. above the cecum. This animal lived ten days, having remained in excellent condition for eight days. The vomiting was not so excessive as in the high obstruction, but was fecal in character and exceedingly offensive after the third or fourth day. The total output of urine and vomitus in ten days was 2,930 c.c., and the saline injections amounted to 3,900 c.c.

Autopsy.—There was no peritonitis. The obstruction was complete, the bowel below the clamp being collapsed and empty. Above the clamp the intestine was distended and filled with foul-smelling fluid feces. There was a slight purplish discoloration of the bowel for about 35 cm. above the obstruction. The mucosa appeared somewhat edematous, but there was no evidence of ulceration or necrosis.

Microscopical Examination.—The intestine shows congestion and edema. There are areas in which some necrosis is present, with exfoliation of the mucosal cells. No pyogenic infiltration is seen.

Liver shows only congestion.

Kidney shows congestion and some parenchymatous degeneration.

DOG 87.—The clamp was applied in the lower ileum. This animal lived in apparent perfect health for eighteen days, when he was killed. The total output of urine and vomitus was 3,950 c.c. and the injections of normal saline totaled 6,600 c.c.

It will be noted that the output of fluids is far less than in the high obstructions, and hence the quantities of saline injected may be reduced.

Autopsy.—There was no peritonitis. The obstruction was complete, the bowel below being empty and collapsed. The bowel above the clamp was moderately distended, but there was an absence of the discoloration, hemorrhages and other evidences of tissue damage seen in the other cases. On opening the intestine the mucosa appeared absolutely normal throughout, except for one small area 5 cm. in diameter, about 20 cm. above the clamp, where there was an ecchymosis.

Microscopical Examination.—The intestine shows only a slight congestion. There is an absence of the lesions found in the animals which died at an early date.

The kidneys and liver are entirely normal.

The study of low obstruction gives, therefore, results exactly like those found in the high obstruction. Dogs may be kept alive indefinitely by the injection of an excess of normal saline solution, if the intestinal wall remains undamaged. Such injections, however, will not save life where there exist lesions in the mucosa which destroy the natural protection against the absorption of bacterial and other poisons from the lumen of the bowel.

It may be asked what actual evidence has been found that poisons enter the system even under these conditions. The evidence is indirect and inferential. It is plain that so long as the mucosa remains intact, and desiccation of the tissues is prevented, there is no absorption of poisons because the animals remain in perfect health. This does not mean that the stagnated intestinal contents would not prove poisonous if they could enter the blood. On the contrary, they are poisonous even after sterilization by boiling and filtering, as many investigators have shown. In every instance, however, in which serious symptoms of sickness develop and ultimately the animal dies, a damaged mucosa is found at autopsy. Study of this lesion shows it to be a destructive one. The mucosa is more or less destroyed and all the evidence is present that there is a bacterial inflammation in the intestinal wall. The severity of the symptoms varies directly and the length of life inversely with the extent of this damage. It is just as certain an inference that some poison is absorbed under these circumstances as any other of the many infective inflammatory lesions which we recognize as being the source of a toxemia, even though a bacteriemia is absent.

There are two points to be explained in comparing the high and low obstruction. First, why do the animals with the latter vomit a less quantity? Second, why cannot all the dogs with a low obstruction be kept alive by the administration of saline solution?

The vomitus is reduced in the low obstruction because there is a long surface of intestine through which absorption takes place. Similarly the dogs are less desiccated because the water content of the bile, gastric and intestinal juices reenter the body. On the other hand, there is practically no absorbing surface available for this purpose in the high obstructions, and the distance backward into the stomach being short, the latter organ rapidly fills and vomiting is imperative and almost incessant.

The explanation of the inability to save life in low obstruction is found in the mechanical conditions which exist. The small intestine above the obstruction becomes distended, and following this, kinking and tension on the mesentery develops. In this way there are areas in which severe circulatory disturbance is present, resulting in the very changes which we have found will cause death and which are uninfluenced by the administration of saline subcutaneously.

The results of our investigations of intestinal obstructions may be summarized as follows:

1. There are two factors at work in producing the symptoms and causing death in this condition.

First, the loss of water from the tissues, due to the excessive drain into the bowel in response to the irritation set up by the retained secretions. This water may be replaced by subcutaneous injection of normal saline solution, and the symptoms caused are thus entirely controlled, with a saving of life.

Second, the entrance into the circulation of poisonous materials, which occurs only when the mucosa of the bowel is damaged. This damage results largely from the trauma inflicted by the overdistention acting on the circulation, but possibly also by the chemical action of the digestive ferments stagnated above the obstruction. Such a damage having resulted, there occurs a bacterial invasion into the bowel wall with a death of tissue cells (which is invariably demonstrable by microscopical examination), and in this process the poisonous substances are elaborated. The action of these poisons is apparently not influenced by the administration of saline subcutaneously.

The absorption of a poison from any source whatsoever, so long as the mucosa remains intact, is not a factor.

2. The development of a bacteriemia as a cause of death is excluded.

CLINICAL APPLICATION

It is not always safe to transfer the findings of experimental work to clinical practice, and as yet we have had no extended opportunity to apply the teaching of our investigations to the bedside. There are certain applications, however, which seem justified. It has always been a matter of speculation why high intestinal obstruction in man is so much more acute than low obstruction. The explanation is found in the fact that water absorption is entirely stopped in the first, and in addition, enormous amounts of water are thrown out in the vomitus almost as soon as the obstruction occurs. A rapid desiccation takes place, and with it a severely damaged metabolism, as shown by the deranged urine output. These conditions obtain much more gradually when the obstruction is low in the bowel. Another factor is also found in the sudden enormous duodenal and gastric distention which mechanically damages the mucosa.

It is a familiar observation that a chronic obstruction may take place in the bowel and progress until the opening is only pin-point in size, yet no serious symptoms arise, even though there may be for many days cessation of fecal passage from the bowels. When, however, a complete closure supervenes, there arises immediate evidence of a severe condition. The well-known symptoms of acute intestinal obstruction are manifest. The explanation of this is found in the fact that so long as gas can escape through the constriction, there is no distention of the intestine, and hence no damage to the intestinal wall, and no absorption of poisonous materials. The stoppage of gas, however, is immediately followed by both these conditions, and unless promptly relieved will result fatally. The practical application of the principles elaborated by the experimental work follows two lines. First, the water extracted from the tissues by the enormous outpouring into the bowel must be replaced. This can easily be done by means of a continuous hypodermoclysis administered under the skin in the pectoral region by use of needles of the ordinary hypodermic caliber, but longer. In this way the fluid is absorbed almost as rapidly as it enters, 1 or 2 liters being given without withdrawing the needles. The absorption will continue until the normal water content of the tissues is reestablished. Since, however, this has no influence on the symptoms resulting from a damaged intestinal wall, it is imperative to relieve the obstruction surgically as early as it is discovered. A second point of practical importance is derived from our experiments, that is, an answer to the question as to the advisability of opening the bowel, and either temporarily or permanently draining off the contents. Whenever there has resulted from the obstruction any considerable damage to the bowel wall above the constricted point, by reason of distention and circulatory changes, there is danger of serious symptoms arising from the absorption of materials resulting from these changes. Therefore, in the presence of such changes, the more rapid emptying of the bowel through an enterostomy than through the normal path, after relieving the obstruction, may be a wise thing to do. Whether the drainage of the intestine shall be made to continue after primarily emptying as much as may be possible of the distended bowel depends on the extent of the damage done. If this is great in amount, it may be advisable to establish an enterostomy, because there will be some farther accumulation of the poisons which will be absorbed unless there is a free exit for them. Such an enterostomy will be necessary if the contents of the bowel above the obstruction are blood-tinged, demonstrating a damage to the bowel wall. If it is simply fluid feces, the rapidly returning peristalsis, after the obstruction is released, will force the contents onward, and there will be no danger of poisonous absorption when once it gets into normal bowel below the obstruction, because the mucosa here possesses a defense against such absorption.

We desire to express our thanks to Drs. Elser, Benedict, Ewing and Lusk of the Cornell University Medical College who gave us many valuable suggestions and material aid in parts of the work here presented.

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THE CLASSIFICATION OF AMEBAS

WITH OBSERVATIONS ON MORPHOLOGY AND LIFE CYCLE OF ENTAMOEBA COLI, CRAIGIA HOMINIS AND VAHLKAMPFIA LOBOSPINOSA *

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Recent observations on the morphology of the amebas encountered in the human intestine, and on their life cycle, have shown conclusively that there are two species of entamebas parasitic in the intestine of man, *Entamoeba histolytica* and *Entamoeba coli*, and that in rare instances species belonging to the genus *Vahlkampfia*, normally free living, may lead a semiparasitic existence in the human intestine for a longer or shorter period of time. In view of these facts it has been necessary to revise our classification of amebas and in the following contribution I have adopted Calkins' classification and have recorded the latest observations on *E. coli*, *Craigia hominis* and *Vahlkampfia lobospinosa*. If some of the statements contained in the paper appear somewhat dogmatic I can only plead in excuse the fact that they are personal opinions based on years of careful study of the organisms in question.

CLASSIFICATION AND NOMENCLATURE

It would be of little interest to describe the efforts made at the classification of the amebas occurring in man prior to the researches of Schaudinn. In 1903[1] he divided these organisms into two species, *E. histolytica* and *E. coli*. At present several classifications are advocated by different authorities and it is difficult to select that which is accepted by the greatest number of protozoologists. The work of Musgrave and Clegg[2] on the cultivation of amebas from man early made it evident that amebas occur in the intestine and in the feces, as well as in the pus of liver abscesses, that were not identical with either *E. histolytica* or *E. coli*, and their conclusion that these cultivated amebas could cause dysentery resulted in the greatest confusion in classification and nomen-

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* From the Department Laboratory, Central Department, U. S. Army.

[1] Schaudinn, F.: Untersuchungen ueber die Fortpflanzung einiger Rhizopoden, Arb. a. d. k. Gsndhtsamte, 1903, xix, 547.

[2] Musgrave, W. E., and Clegg, M. T.: Amebas: Their Cultivation and Etiologic Significance, Bull. Govt. Lab., Biolog. Lab., Manila, 1904, 18.

clature. The work of Hartmann[3] and Whitmore,[4] as well as that of many other investigators, in proving that these cultivated amebas are not entamebas at all and have nothing to do with the production of dysentery, has resulted in a clearer conception of the entire question of classification of the parasitic amebas, or entamebas, and their relation to infection and the production of disease.

At present it is admitted that the old genus *Amoeba* should be split into several genera, some of these living free in nature, while others are either partly or wholly parasitic in their life habits. It is also recognized that some of the free-living forms frequently contaminate the food of man and thus reach the intestinal canal, where they may be demonstrated in the feces, generally in the encysted stage of development, but sometimes as vegetative forms, and it is believed that certain of these free-living species may actually become temporary parasites of man or other animals. The amebas that have been cultivated from the feces belong to these free-living species, and have either reached the feces through being swallowed in infected food or water, or by aerial contamination. These species differ entirely from the entamebas both in morphology and life history. Although under the action of certain stimulins in artificial culture-mediums these organisms may show developmental stages similar to those observed in entamebas, and their morphology may become markedly modified, as proved by Calkins and Williams,[5] a careful study of these modified organisms will show that, after all, the nuclear structure is quite different from that of either *E. histolytica* or *E. coli,* and that there is no reason to believe that the latter species ever are transformed into the free-living species. That the genus *Vahlkampfia* contains species that can be cultivated from the intestine or feces of man is undoubted, and that under cultivation these species may undergo marked modifications in morphology and life history is true, but that they are identical with true entamebas is disproved by the observations of nearly all authorities who have worked with both genera.

The modern classification of amebas has been attempted by many protozoologists, and Chatton,[6] Alexeieff,[7] Doflein,[8] and Hartmann[3] have each proposed classifications that possess advantages. In this paper,

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[3] Hartmann, M.: Article "Die Dysenterie Amoeben" in Von Prowazek's Handbuch der Pathogenen Protozoen, 1912, i, 51.

[4] Whitmore, E. R.: Parasitaire und Freilebende Amoeben aus Manila und Saigon, etc., Arch. f. Protistenk., 1911, xxiii, 71.

[5] Williams, Anna, and Calkins, G. N.: Cultural Amoebae, a Study in Variation, Jour. Med. Research, 1913, xxix, 43.

[6] Chatton, E., and Lalung-Bonnaire, P.: Amibe limax (Vahlkampfia n. gen.) dans l'intestin humaine, Bull. Soc. path. exot., 1912, v, 13.

[7] Alexeieff, A.: Sur les caractères cytoligiques et la systématique des amibes du groupe Limax, Bull. Soc. zool. de France, 1912, v, 55.

[8] Doflein, F.: Lehrbuch der Protozoenkunde, edit. 3, 1911, p. 560.

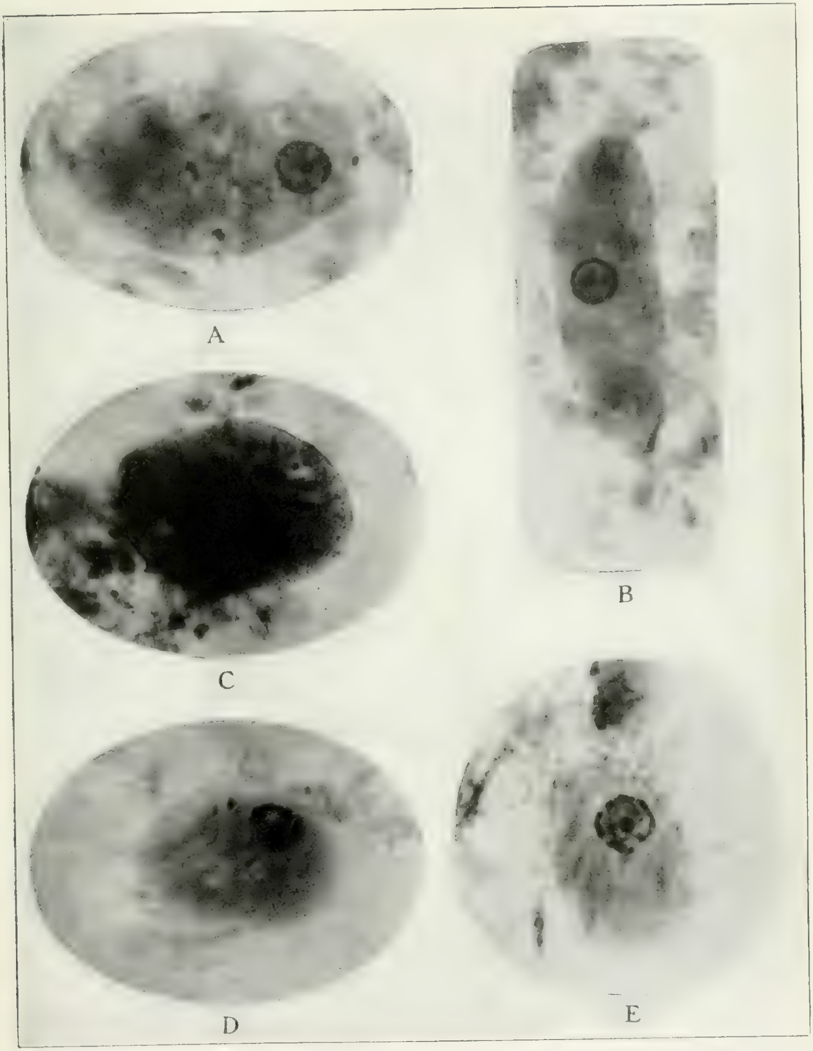

Fig. 1.—Vegetative forms of *Entamoeba coli;* from photomicrographs × 1,200: all specimens stained by Mallory's ferric-chlorid-hematoxylin method. *A*, large-sized organism with characteristic nucleus; *B*, type of nucleus before division begins; *C*, typical nucleus; *D*, nucleus with chromatin on inner border of nuclear membrane; *E*, typical karyosome, granular appearance of the nuclear membrane, linin net-work and intranuclear chromatin.

however, I shall follow the clasification adopted by Calkins,[9] because I believe it to be the most logical at the present stage of our knowledge of the amebas. It must be remembered, however, that any classification, at present, must be purely tentative until the life cycle of every organism contained in it is known, and this is true of only a very few of the so-called species of amebas. It should, therefore, be clearly understood, that while I adopt for the present the classification of Calkins, and while I shall list all described species of amebas under their respective genera in this classification, I believe that in time it will have to be changed, and that many of the described species will eventually be found to be identical with those better known.

Calkins divides the old genus *Amoeba* into seven genera, as follows: *Amoeba, Vahlkampfia, Nagleria, Paramoeba, Craigia, Trimastigamoeba,* and *Entamoeba.* Of these seven genera the only ones of interest to us in our discussion of the parasitic amebas of man are: *Vahlkampfia, Craigia, Trimastigamoeba* and *Entamoeba.*

Genus *Vahlkampfia*, Chatton, 1912: Chatton established this genus in 1912, as containing certain small amebas originally classed in the genus *Amoeba* under the so-called limax type, and excluding organisms having a flagellate stage of existence.

Amebas of this genus are characterized by the presence in each of one or more nuclei and one or more contractile vacuoles. They divide by simple division or a primitive form of mitosis, forming a uninucleate cyst. Under certain abnormal cultural conditions the cyst may contain more than one nucleus, and marked morphological changes may occur in the nucleus (Craig). The nucleus in the vegetative stage contains a very large karyosome which sometimes shows a distinct centriole. Habitat: water, earth, and occasionally in man or other animals.

The following species are included in this genus:

Vahlkampfia limax, Dujardin, 1841; habitat, fresh water.
Vahlkampfia guttula, Dujardin, 1841; habitat, pond-water.
Vahlkampfia polypodia, Schultz, 1875; habitat, pond-water.
Vahlkampfia binucleata, Gruber, 1884; habitat, pond-water.
Vahlkampfia diploidea, Hartmann and Nagler, 1908; habitat, garden earth.
Vahlkampfia albida, Nagler, 1909; habitat, garden earth.
Vahlkampfia horticola, Nagler, 1909; habitat, garden earth.
Vahlkampfia lacustris, Nagler, 1909; habitat, fresh water.
Vahlkampfia froschi, Hartmann, 1907; habitat, fresh water.
Vahlkampfia lacertae, Hartmann, 1907; habitat, in intestine of lizards.
Vahlkampfia mucicola, Chatton, 1909; habitat, ectoparasitic on fish.
Vahlkampfia paedophthora, Caullery, 1910; habitat, eggs and embryos, crabs.
Vahlkampfia tachypodia, Glaser, 1912; habitat, pond-water.
Vahlkampfia lamellipodia, Glaser, 1912; habitat, pond-water.
Vahlkampfia lobospinosa, Craig, 1912; habitat, ditch-water.
Vahlkampfia whitmorei, Hartmann, 1913, habitat, swamp-water.

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[9] Calkins, G. N.: Genera and Species of Amoeba, Tr. Fifteenth Internat. Cong. Hyg. and Demog., 1912, ii, 287.

While most of the species so far described in this genus are free living, there is excellent evidence on record that some of them may become parasitic under certain conditions. Of those mentioned in the list, the one described by Hartmann as *Vahlkampfia lacertae* is certainly a parasitic species, as are *V. mucicola* and *V. paedophthora*. Several observers have already noted the occurrence of typical *Vahlkampfiae* in the feces of man in both the vegetative and cystic stages of development, when the question of outside contamination could be eliminated. I have seen some beautiful preparations containing a typical *Vahlkampfia* obtained by Dr. W. M. James from the feces of a patient observed at Panama. The organisms are in both the vegetative and cystic stages of development and were observed over a considerable period of time, so that the question of contamination of the feces was ruled out. It is interesting to observe that these amebas were easily distinguishable from either *E. histolytica* or *E. coli* in both the vegetative and encysted stages of development.

It is probable that nearly all species of *Vahlkampfia* may be cultivated on artificial mediums, and it is this fact that has given rise to so much confusion regarding the cultivation of the true parasitic amebas. These organisms frequently contaminate fecal or other material derived from patients suffering from entamebic dysentery, and may thus be obtained in cultures. Amebas belonging to this genus have been cultivated by many observers, notably Musgrave and Clegg,[2] in impure culture, and by Williams[10] in pure culture, but the claims made by these investigators that the amebas so cultivated are identical with the true entamebas are unsupported by any adequate evidence. It is now admitted by all competent observers that neither *E. histolytica* nor *E. coli* has been cultivated.

The *Vahlkampfia* named in the above list as *Vahlkampfia lobospinosa* is a true free-living ameba that was first cultivated by Musgrave and Clegg from the feces of a dysentery patient. It has since been obtained in pure culture by Williams. This organism, as shown by Calkins and Williams,[5] when growing in pure culture, undergoes marked morphological and cyclical changes in response to certain cultural conditions, but in the human feces it possesses the morphology of a true *Vahlkampfia,* and even in the cultures is not indistinguishable from the entamebas found in man, as is well shown in the photomicrographs accompanying the paper by these observers. This species has been under cultivation for several years, and the cysts have been found to resist drying for over one year, a fact that alone proves it to be entirely distinct from the entamebas of the intestine of man, for all the evidence of recent researches proves that the cysts of these entamebas have comparatively little resistance.

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[10] Williams, Anna: Pure Cultures of Amoebae Found in Intestines of Animals, Studies Research Lab., New York Board of Health, 1912, vi, 298.

While, as has been stated, species belonging to this genus have been observed apparently parasitic in man, and while, in some cases, they may be cultivated from the feces, the pus of liver abscesses, and other sources, there is no evidence that demonstrates that they are pathogenic or that they can live for any considerable time within the human intestine. In the vast majority of instances they reach the material from which they are cultivated from the air, as proved by Liston[11] and Wells,[12] or by passing through the intestinal canal in contaminated food or water, generally in the encysted condition. It is true that, in rare instances, species of *Vahlkampfia* may become parasitic for a short time in the human intestine, but this is really an abnormal mode of existence, no symptoms of disease are produced, and they may be easily distinguished from the true entamebas by the large nuclear karyosome, the uninucleate cyst, and the presence of at least one contractile vacuole. Their presence in the intestine is chiefly of interest from the point of view of evolution, as indicating the possible origin of the true parasitic amebas.

Genus *Craigia*, Calkins, 1912: In 1912 Calkins[9] established the genus *Craigia* to include the ameba described by myself under the name *Paramoeba hominis*, in 1906. This ameba was originally placed in the genus *Paramoeba* because of its resemblance to Schaudinn's *Paramoeba eilhardi*, but Calkins has shown that it should be placed in a new genus, an opinion previously expressed by Doflein.[8]

The type-species of this genus is *Craigia hominis* (*Paramoeba hominis*) a parasitic ameba that I have observed in twelve patients suffering from a chronic form of diarrhea. It is characterized by a nucleus, an accessory nuclear body, and by an ameboid and flagellate stage of development. Multiplication occurs in the ameboid stage by simple division and by the formation of cysts containing numerous minute flagellated organisms. In the flagellate stage of development multiplication occurs by longitudinal division, preceded by division of the accessory body and the nucleus. Habitat, the intestine of man.

The following species are included in this genus:

Craigia hominis, Craig, 1906; emend. Calkins, 1912.
Craigia pigmentifera, Grassi, 1881; habitat, body cavity of *Chaetognathi.*
Craigia chaetognathi, Grassi, 1881; habitat, body cavity of *Chaetognathi.*

It is interesting to note that all of the species so far described for this genus are parasitic, *Craigia hominis* being parasitic in man, while

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[11] Liston, W. Glen: A Note on Early Stages of Nuclear Division, Quart. Jour. Micr. Sc., 1911, lvii, 279.

[12] Wells, R. T.: Aerial Contaminations as a Fallacy in the Study of Amoebic Infections by Cultural Methods, Parasitology, 1911, iv, 204.

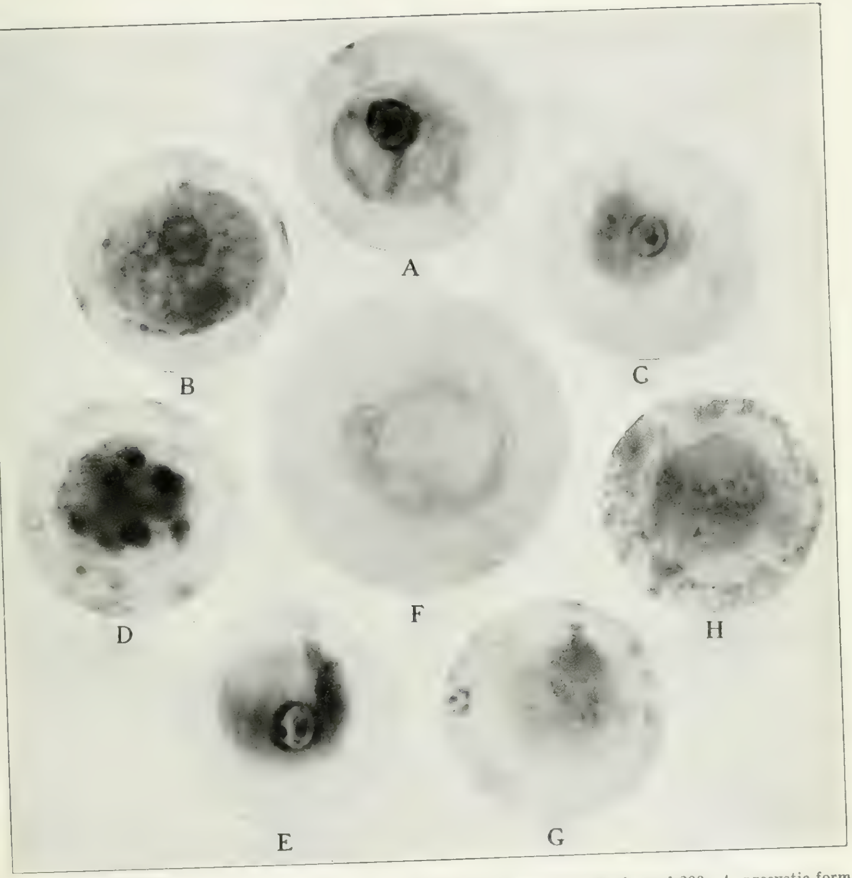

Fig. 2.—Precystic and cystic form of *Entameba coli;* from photomicrographs × 1.200: *A*, precystic form in which the nucleus is more than usually typical; *B*, division of the karyosome into two portions; *C*, precystic form showing change in type of nucleus and slight elongation of karyosome; *D*, precystic form containing yeast cells; *E*, typical cyst showing nucleus in which the karyosome has apparently divided; *F*, very large cyst showing large vacuole and nucleus in which the karyosome has elongated preparatory to division; *G*, cyst containing six nuclei; eight were present but two are out of focus; *H*, cyst containing three definite nuclei. Four were present, but one does not show as it lies out of focus.

Craigia pigmentifera and *Craigia chaetognathi* are both parasitic in certain species of marine worms.

This genus is of considerable interest to the physician, as it contains a species which, during the ameboid stage, may be easily confused, by one unfamiliar with the protozoa of the intestine, with amebas belonging to the genus *Vahlkampfia* or *Entamoeba*, and in the flagellate stage with *Trichomonas hominis* or other intestinal flagellates. This mistake, however, could never be made by any one well acquainted with the morphology of the parasites mentioned.

Genus *Trimastigamoeba*, Whitmore, 1911: Whitmore[13] established this genus, in 1911, to include an ameba isolated by himself in cultures from tap-water, in Manila. The type-species is *Trimastigamoeba philippinensis*, and is characterized by a nucleus of the limax type, a contractile vacuole, and the occurrence, under certain conditions, of flagellate forms having three equal flagella. The species is easily cultivated on suitable mediums, and is the only one so far placed in the genus. This ameba is of interest to physicians, because it may contaminate fecal or other material from human sources and appear in cultures prepared from such material. There is no evidence that this species occurs as a parasite in man or other animals.

Genus *Entamoeba*, Leidy, 1879: This genus, which contains most of the parasitic amebas of man and other animals, was established in 1879 by Joseph Leidy,[4] who used the spelling *Endamoeba* in the description of the genus. The type-species is *Entamoeba blattae*, a parasite of the cockroach. Casagrandi and Barbagallo,[15] in 1897, unaware of Leidy's genus *Endamoeba*, established for the parasitic amebas the genus *Entamoeba*, and this is the spelling employed at present.

The generic characters are as follows: Size comparatively small, from 5 to 80 microns. Ectoplasm and endoplasm distinct when the organisms are moving and often when motionless; contractile vacuole generally absent; nucleus with definite karyosome and centriole; nuclear division mesomitotic and mitotic; reproduction by simple division, schizogony, and cyst formation with the production of several amebas within the cyst. Habitat, the body of man or other animals, generally in the digestive tract. The genus contains only parasitic species, some of which are pathogenic, but most live merely as commensals in the intestine of their host. None of the species have been artificially cultivated.

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[13] Whitmore, E. R.: Studien über Kulturamoeben aus Manila, Arch. f. Protistenk., 1911, xxiii, 81.

[14] Leidy, Joseph: Fresh-Water Rhizopods of North America, Rep. U. S. Geol. Surv., Washington, 1879, xii, 1.

[15] Casagrandi, O. G., and Barbagallo, P.: Richerche biologiche e cliniche sull' Amoeba colix, Boll. d. Accad. Gioenia di sc. nat. in Catalonia, n. s., 1895, xxxix, 4.

A very large number of species of amebas have been placed in this genus, and new species are being discovered almost monthly, but, as I have already stated, further study will prove many of these to be identical with species already studied. I have placed in the list that follows, however, all the species reports of which I have been able to collect in the literature, but I have indicated those identified with other species. The list is arranged alphabetically, and the name of the host follows that of the parasite.

Entamoeba africana, Hartmann, 1907: identical with *Entamoeba histolytica;* host, man.

Entamoeba blattae, Leidy, 1879; host, cockroach.

Entamoeba aulastomi, Noller, 1912; host, eagle.

Entamoeba bovis, Liebetanz, 1905; host, cattle.

Entamoeba brasiliensis, Baurepaire Aragao, 1912; host, man.

Entamoeba buccalis, von Prowazek, 1907; host, man.

Entamoeba butschlii, von Prowazek, 1912; host, man.

Entamoeba cobayae, Walker, 1908; host, guinea-pig.

Entamoeba coli, Loesch, emend. Schaudinn, 1903; host, man.

Entamoeba dentalis, Braun, 1883; identical with *E. buccalis;* host, man.

Entamoeba duboscqi, Mathias, 1913; emend. Craig, 1913; host, monkey.

Entamoeba dysenteriae, Councilman and Lafleur, emend. Craig, 1905; identical with *E. histolytica;* host, man.

Entamoeba gingivalis, Braun, 1895; identical with E. buccalis; host, man.

Entamoeba hartmanni, von Prowazek, 1912; host, man.

Entamoeba histolytica, Schaudinn, 1903; host, man.

Entamoeba intestinalis, Walker, 1908; host, cat.

Entamoeba kartulisi, Doflein, 1901; host, man.

Entamoeba lacertae, Hartmann, 1907; identical with *Vahlkampfia lacertae;* host, lizard.

Entamoeba lagopidis, Fantham, 1910; host, moor hen.

Entamoeba legeri, Mathias, 1913, emend. Craig, 1914; host, monkey.

Entamoeba maxillaris, Kartulis, 1906; identical with *E. kartulisi;* host, man.

Entamoeba minuta, Elmassian, 1909; identical with *E. histolytica*; host, man.

Entamoeba miurai, Ijima, 1898; host, man.

Entamoeba mortinatalium, Smith and Weidman, 1910; host, man.

Entamoeba muris, Grassi, 1881; host, mouse.

Entamoeba nipponica, Koidzumi, 1909; identical with *E. coli;* host, man.

Entamoeba nuttalli, Castellani, 1908; host, monkey.

Entamoeba phagocytoides, Gauducheau, 1907; host, man.

Entamoeba pitheci, von Prowazek, 1912; host, monkey.

Entamoeba polecki, von Prowazek, 1912; host, swine and man.

Entamoeba pulmonalis, Artault, 1898; host, man.

Entamoeba ranarum, Grassi, 1879; host, frog.

Entamoeba salpae, Alexeieff, 1912; host, fish.

Entamoeba schaudinni, Lesage, 1908; host, man.

Entamoeba suis, Hartmann; host; swine.

Entamoeba testudinis, Hartmann, 1910; host, turtle.

Entamoeba tetragena, Viereck, 1907; identical with *E. histolytica*; host, man.

Entamoeba tropicalis, Lesage, 1908; identical with *E. coli*; host, man.

Entamoeba undulans, Castellani, 1904; host, man.

Entamoeba urogenitalis, Baelz, 1883; host, man.

Entamoeba williamsi, von Prowazek, 1911; host, man.

It is more than probable that at least two-thirds of these species here given as parasitic in man are not valid species, but, as I have not had the opportunity of studying them, I include in the list all of the species of entamebas that have been described. Of these, however, there are really only two species that are of great interest to the physician; that is, *E. histolytica* and *E. coli;* the former is the common pathogenic species causing entamebic dysentery and liver abscess in man, while the latter is a harmless commensal, found in a varying, but usually large proportion of healthy, as well as diseased individuals, in almost every part of the world.

A word of explanation is necessary in regard to the classification of the so-called *E. tetragena.* This entameba was first described by Viereck,[16] in 1907, as a distinct species causing dysentery in man, and his observations were quickly confirmed by Hartmann[3] and Prowazek, Whitmore,[17] and myself;[18] but recent researches have proved conclusively that this species is really identical with *E. histolytica,* a portion of the life cycle of the latter species having been erroneously described by Schaudinn and his followers, and first correctly described by Viereck in his description of *E. tetragena.* It therefore follows that *tetragena* ceases to exist as a distinct species and the name must be eliminated from our nomenclature.

It has also been shown that *E. minuta* is identical with *histolytica,* and that *E. nipponica* and *E. tropicalis* are identical with *E. coli,* so that these three names also should be eliminated as specific names of entamebas.

Since the discovery that *E. tetragena* was identical with *E. histolytica,* the credit for which belongs to Walker,[19] nearly all students of the subject who have had sufficient material on which to work are agreed that two well-defined species of entamebas occur in the intestine of man. Since 1905 I have consistently maintained the specificity of these two entamebas; that is, *E. histolytica* and *E. coli,* and in my first paper,[20] and since, have insisted that it is possible to differentiate them in practically every case of infection. Many observers have confirmed my conclusions, but the recent work of Walker and Sellards[21] has conclusively proved my statements regarding the pathogenic nature of *histolytica* and the non-pathogenicity of *coli,* and also my conclusions regarding the lack of identity of cultural amebas and those parasitic in man. By experiments on man these authors have proved that the amebas that can be cultivated from water, from the feces of man and other animals, and from other sources, are incapable, when ingested, of producing lesions in man, and that they are not entamebas but free-living amebas which do not produce dysentery, while, as already stated, their experiments prove

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[16] Viereck, H.: Studien über die in den Tropen erworbene Dysenterie, Arch. f. Schiffs u. Tropen-Hyg., 1907, ii, 1.

[17] Whitmore, E. R.: Parasitaire und freilebende Amoeben aus Manila und Saigon, Arch. f. Protistenk., 1911, xxiii, 71.

[18] Craig, Charles F.: Entamoeba Tetragena as a Cause of Dysentery in the Philippine Islands, The Archives Int. Med., 1911, vii, 362.

[19] Walker, E. L.: A Comparative Study of the Amoebae of the Manila Water-Supply, etc., Philippine Jour. Sc., Med. Sec., 1911, vi, 259.

[20] Craig, Charles F.: Observations Upon Amebas Infecting the Human Intestine, with a Description of Two Species, Entamoeba Coli and Entamoeba Dysenteriae, Am. Med., Philadelphia, 1905, ix, 854, 897 and 936.

[21] Walker, E. L., and Sellards, A. W.: Experimental Entamoebic Dysentery, Philippine Jour. of Sc., Sec. B, Trop. Med., 1913, viii, 253.

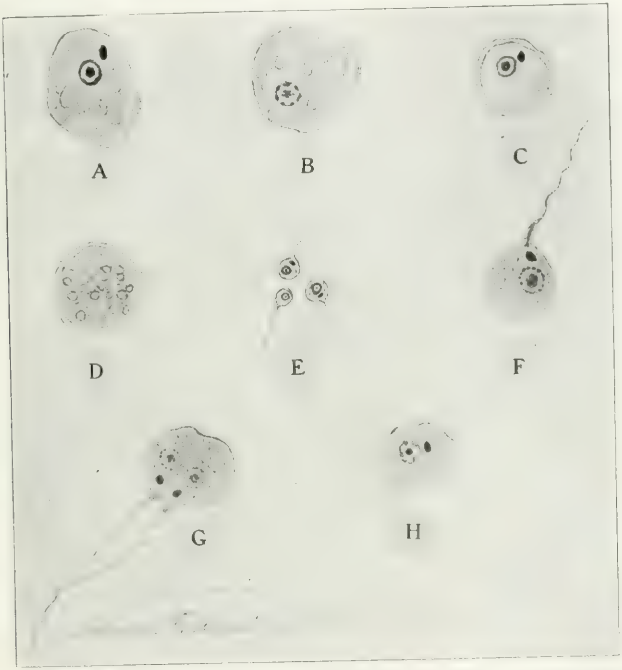

Fig. 3.—*Craigia hominis*, from pencil drawings. × 1,200. *A*, typical organism in amebic stage (note structure of nucleus and accessory nuclear body); *B*, absence of accessory nuclear body and different type of nucleus; *C*, cyst showing one nucleus; *D*, cyst showing granular appearance of cytoplasm and the presence of numerous nuclei; *E*, young flagellate form; F, fully developed flagellate form. (Note absence of undulating membane, the single flagellum, the nucleus, and accessory nuclear body); *G*, dividing flagellated form the flagellum being partly divided, while the nucleus and accessory nuclear body have divided; *H*, flagellate form after loss of flagellum and just before becoming ameboid.

that *E. histolytica* produces dysentery in man, and *E. coli* is a harmless commensal in the human intestine. While all of the essential points covered in Walker and Sellard's work have been previously proved by experiments on the lower animals, their results possess the very great advantage of having been worked out on man, the natural host of *histolytica* and *coli,* and, in my opinion, settle for all time the question of the relation of parasitic and cultural amebas to disease in man.

At present a considerable amount of controversy has arisen regarding the proper name for the common dysentery-producing entameba, usually known as *E. histolytica.* The name *tetragena* must be dropped as a specific name, although it may be used to designate the type of nucleus present during certain developmental stages of *histolytica.* This conclusion is admitted by nearly all protozoologists; but Doflein and Hartmann favor substituting the specific name *dysenteriae* for *histolytica,* this name having been first proposed for the dysentery entameba by Councilman and Lafleur. This is not a new proposition, for in 1905[20] I suggested that the name *dysenteriae* be given this entameba, but, as Stiles later showed that this name was merely a synonym of *coli,* and as Schaudinn had already used *coli* as the specific name for the harmless entameba of man, I adopted his name, *E. histolytica,* for the pathogenic species.

While it is undoubtedly true that Councilman and Lafleur described *E. histolytica* in part in their exhaustive work on entamebic dysentery, it is perfectly evident to any one who studies their description carefully that they confused this parasite with the harmless *E. coli,* and failed to differentiate between the pathogenic and harmless entamebas or to give morphological data sufficient to enable such a differentiation to be made by other workers. In view of these facts and the fact that Schaudinn *did* differentiate the two species mentioned, I am convinced that, if we are to be consistent in our nomenclatural rules, the name *E. histolytica,* given by him to the pathogenic species, must be retained. The name *dysenteriae* is a much more descriptive and appropriate name, but if we are to be true to the accepted rules of nomenclature it cannot justly be applied to the entameba now known as *E. histolytica.*

OBSERVATION ON E. COLI, LOESCH, 1875; EMEND. SCHAUDINN, 1903

It was long known that amebas were frequently present in the feces of healthy persons and in those of patients suffering from other diseases than dysentery, Grassi[22] being one of the first to describe these amebas. His work was followed by that of Calandruccio,[23] Schuberg,[24] Strong and

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[22] 22. Grassi, G. B.: Dei Protozoi parasiti e specialmente di quelli che sons nell' uomo, Gaz. Med. ital., Lombardie, 1879, xxxix, 445.

[23] 23. Calandruccio, S.: Animali parasiti dell' uomo in Sicilia, Atti d. Accad. Gioenia di sc. nat. in Catania, 1889, lxvi, 95.

[24] 24. Schuberg, A.: Die parasitischen Amoeben des menschlichen Darmes, Centralbl. f. Bakteriol., 1893, xiii, 598, 654 and 701.

Musgrave,[25] and Casagrandi and Barbagallo.[15] In 1903, Schaudinn[1] accurately described this entameba, and his observations were confirmed by myself in 1905.[26] Important papers dealing with this parasite have since appeared by Werner[27] and Hartmann and Whitmore.[28]

Several observers since Schaudinn have described as new species entamebas occurring in healthy, as well as diseased individuals, that answer closely to the description of *E. coli.* Among these may be mentioned *E. tropicalis*, described by Lesage[29] in 1908; *E. nipponica*, described by Koidzumi[30] in 1909, and *E. williamsi*, described by von Prowazek[31] in 1911. Recent observations have shown that all these so-called species are identical with *E. coli*, and it is probable that some other species of entamebas that have been described in the intestine of man are also identical with this parasite.

The recognition of this species is of great importance because of its world-wide distribution, the fact that it is a harmless parasite, and the possibility of confusing it with the pathogenic *E. histolytica.* Our statistics of the actual occurrence of entamebic dysentery in all parts of the world are greatly vitiated by the non-recognition of this harmless species, many authorities making a diagnosis of entamebic dysentery whenever an ameba was found in the stools, without regard to the species present. It is now evident that a diagnosis of entamebic dysentery based on anything less than the recognition of *E. histolytica* in the feces cannot be considered as authentic, and if this test had been applied to the diagnosis of the disease in the past it is probable that our conceptions of its frequency in certain localities would be greatly modified.

E. coli has a very wide geographical distribution, being most frequently observed in tropical and subtropical regions, but being by no means infrequent in the temperate zones. In discussing the relation of this organism to disease the distribution will be more fully considered, but it may be stated here that it has been found wherever determined efforts have been made to demonstrate it, and this fact makes its recognition of prime importance in the discussion of entamebic infection.

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[25] Strong, R. T., and Musgrave, W. E.: Preliminary Note Regarding the Etiology of the Dysenteries of Manila, Rep. Surg. Gen. U. S. Army, 1900, p. 251.

[26] Craig, Charles F.: Observations Upon Amoebae Infecting the Human Intestine, Etc., Am. Med., Philadelphia, 1905, ix, 854, 897 and 936.

[27] Werner, H.: Entamoeba Coli, Handbuch der path. Protozoen, von Prowazek, i, 67.

[28] Hartmann, M., and Whitmore, E. R.: Untersuchungen über Parasitische Amoeben: Entamoeba coli, Arch. f. Protistenk., 1912, xxiv, 182.

[29] Lesage, A.: Culture de l'amibe de la dysenterie des pays chauds, Ann. de l'Inst. Pasteur, 1909, xviii, 9; Bull. Soc. de path. Exot., 1908, v, 104.

[30] Koidzumi, M.: On a New Parasitic Amoeba, Entamoeba Nipponica, found in the Intestine of Japanese, Centralbl. f. Bakteriol., Orig. 1909, li, 650.

[31] Von Prowazek, S.: Beitrage zur Entamoeba Frage (Entamoeba williamsi), Arch. f. Protistenk, 1911, xxii, 345.

Morphology.—Like *E. histolytica,* this species varies greatly in morphology at different stages in its life cycle, and this cycle may also be divided into the vegetative stage, the precystic stage and the cystic stage, in each of which a description of the special morphology is necessary.

Morphology in the Vegetative Stage.—In this stage of development *E. coli* varies greatly in size, very large and very small organisms being frequently observed in the same preparation. The living vegetative parasites vary from 15 to 50 microns in diameter, and rarely may be larger, but the average diameter is about 25 to 35 microns. The cytoplasm is divided into two portions, the ectoplasm and endoplasm, but the distinction is not possible save when the organisms are moving. In this species the ectoplasm does not have the glass-like appearance of the ectoplasm of *E. histolytica,* but approaches much more closely to the endoplasm in appearance, so that even when moving the ectoplasm is not nearly as distinct in *coli* as it is in *histolytica,* a very valuable differential point. The *cytoplasm* contains a visible nucleus, appearing as a spherical body bounded by a refractile granular membrane and containing granules or small masses of refractile chromatin, generally arranged as a well-marked karyosome. The nucleus of this species, even in the living condition, appears larger than does the *tetragena* type of nucleus of *E. histolytica,* and this is more easily demonstrated in the living parasite. The endoplasm appears very granular and contains numerous vacuoles, bacteria, and crystals taken up from the feces. In contradistinction to *E. histolytica,* this parasite is not phagocytic for red blood-corpuscles, even when the feces contain much blood, nor have I been able to demonstrate this phenomenon by adding fresh blood to feces containing *E. coli,* although phagocytosis of the blood-corpuscles may often be observed if blood be added to fecal material containing *E. histolytica.* I have observed very rarely an entameba of this species with one or two red blood-corpuscles within the endoplasm, but I have never observed them filled with erythrocytes as in the case of *histolytica,* and I believe that when this process does occur in *coli* it is purely accidental, while in *histolytica* it is a normal process in the nutrition of the organism. At any rate, the point is of great value in the differentiation of the two species, for one is quite safe in regarding any entameba containing red blood-corpuscles as a pathogenic parasite, presumably *E. histolytica.*

The motility of *E. coli,* in the vegetative stage, is much less marked than that of *E. histolytica,* although it may be quite active in the larger organisms in freshly voided feces. To one who has had experience in the study of living specimens of both species, the difference in motility is very marked, *E. coli,* even when most active, being sluggish in comparison with the average vegetative specimen of *E. histolytica.* The movement is also less progressive in character and more apt to be indefinite in direction.

In stained preparations, (wet fixation and iron-haematoxylin) during the vegetative stage of development, the cytoplasm stains a brownish or grayish color and appears granular in consistence, containing bacteria, crystals, and generally a considerable number of vacuoles, but the most striking object is the nucleus, which in this species is much larger than either the histolytica or tetragena type of nucleus of *E. histolytica*, in the vast majority of organisms examined, and much richer in chromatin. The nucleus is spherical and situated within the endoplasm. The nuclear membrane is thick and stains intensely black with hematoxylin. It is even thicker than the membrane of the tetragena type of nucleus in *E. histolytica* and presents on its inner surface granules, or more frequently, clumps of chromatin. The

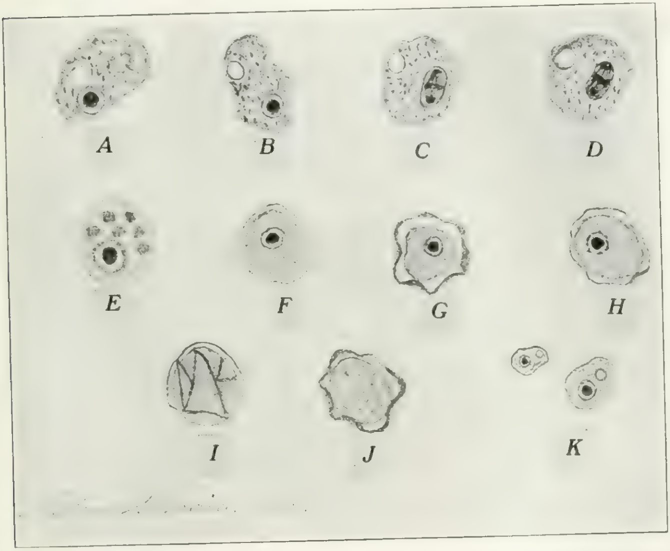

Fig. 4.—Vegetative forms of *Vahlkampfia lobospinosa*, from pencil drawings. × 1,200: *A*. shows large contractile vacuole near the nucleus, and typical nucleus (note the large, deeply staining karyosome); *B*, the contractile vacuole near the periphery of the cytoplasm; *C*, division of the nucleus; note the polar bodies and equatorial plate; *D*, nuclear division; *E*, organism containing yeast-cells; note the granular appearance of the nuclear membrane; *F*, typical young cyst; *G*, old cyst; note thick cyst-wall which is folded in places, a very characteristic appearance of the old cysts; *H*, *I*, *J*, cysts; *I* and *J*, degenerated, the nucleus having disappeared; *K*, young organisms shortly after liberation from cyst.

karyosome is situated at or near the center of the nucleus and appears most frequently as a spherical mass of chromatin, stained almost black, and containing no well-defined centriole. In some instances a centriole may be distinguished as a more deeply staining dot of chromatin near the center of the karyosome. In this species a certain series of cyclical changes occur in the nucleus, but they are not so pronounced as in the nucleus of *E. histolytica*, when the tetragena type is present. It is noted that when there is a large, spherical, solid-appearing karyosome there is little evidence of a linin network or of free chromatin within the nucleus, while the inner surface of the nuclear membrane is almost free from granules of chromatin; but when division of the karyosome occurs, this portion of the nucleus appears smaller and stains less intensely, while the linin network is more distinct, contains much chromatin in the form of small granules, and large clumps of this substance may be observed on the inner surface of the nuclear membrane. The large clumps of chromatin just mentioned are quite characteristic of this species, for I have never observed such large masses on the nuclear membranes of the pathogenic species.

Not infrequently specimens of *E. coli* are observed undergoing simple division, and in stained preparations it is possible to study this process from the initial division of the centriole to the complete division of the nucleus. Very frequently organisms are observed in which the karyosome consists of two deeply stained oval masses of chromatin situated near the center of the nucleus or near its periphery, these masses sometimes being connected by a dimly stained thread of chromatic substance. More frequently the masses are apparently separate and either oval or spindle-shaped, while the interval between them appears dimly granular; but I have never observed any evidences of an equatorial plate. Other organisms are observed in which the karyosome has disappeared and the inner surface of the nuclear membrane is covered with large, irregular clumps of chromatin, the remainder of the nucleus being filled with fine, dimly staining granules; and still others are observed containing two well-developed nuclei, each showing the large, spherical, deeply stained karyosome characteristic of the nucleus of this species before the changes prior to division occur.

Besides the reproduction of the organism by division, Schaudinn described, in the vegetative stage of development of *E. coli*, a process of schizogony, in which the parent entameba produced eight young entamebas. I confirmed this observation and Hartmann and Whitmore[28] have published beautiful illustrations of vegetative organisms containing as many as six nuclei. In my experience, this method of reproduction is very rarely observed, but I am convinced that it occurs and that the organisms in which I have observed it were not in the cystic stage of development. The process is initiated by an enlargement of the nucleus and a considerable increase in the amount of chromatin within it, the karyosome being indistinguishable. Later the inner border of the nuclear membrane shows hemispheral masses of chromatin, arranged in a very regular manner, the remainder of the nucleus being entirely free of this substance. Organisms are observed containing from two to eight nuclei, each nucleus having a distinct nuclear membrane and a small, dot-like or granular appearing karyosome. This method of reproduction has been questioned by several observers, notably James, but, in my opinion, no other interpretation can be placed on these organisms.

Degenerative forms of *E. coli* are frequently encountered during the vegetative stage of development, which may cause confusion in the diagnosis of the parasite. In such organisms the nucleus may be invisible or distorted in appearance, and the cytoplasm may contain chromidia, as in *E. histolytica.* These organisms should not be considered in making a diagnosis of the species of entameba present, for typical parasites will always be found in stained preparations if carefully searched for, and the technic of staining has been correct.

In some preparations entamebas are observed without a nucleus and free nuclei may be present in large numbers. These free nuclei stain well and are typical in structure, and the exact significance of their occurrence is still in question. This peculiar phenomenon was first called to my attention by James, who sent me preparations containing many examples of anucleate entamebas and free nuclei, and I have no explanation to offer of their presence, beyond the suggestion that possibly they may be due to some change brought about in fixing the preparation or in smearing it on the slide. I do not believe that the condition is due to degenerative changes, for the nuclei appear normal as do the anucleate entamebas.

The vegetative forms of *E. coli* occur most typically in diarrheal stools or stools rendered liquid by some cathartic and, as this parasite is not pathogenic in character, these forms are seldom observed in the normal formed stools of the host, only the precystic or cystic forms being found in semiformed or formed stools. For this reason I have found that the administration of a cathartic is essential if one desires to study the typical vegetative stage of *E. coli,* but inadvisable if one desires to study the precystic or cystic stage. It is unfortunate that the differentiation of *E. coli* is of the greatest practical importance in just the class of cases in which the vegetative forms occur, that is, in cases showing diarrhea, for the vegetative forms are much harder to differentiate from the vegetative forms of *E. histolytica* than are the cysts of the two species.

Morphology in the Pre-Cystic Stage.—In semifluid stools the precystic forms of *E. coli* are most frequently encountered. In this stage of development the parasite is reduced in size and resembles so closely the precystic stage of *E. histolytica* as in many instances to be almost indistinguishable.

In the living specimen, the shape is usually oval or spherical, but irregular if motility is present. The size varies from 8 to 15 microns, the average being about 12 microns. Motility is very sluggish, very rarely progressive, and generally consists in the sending out of small, blunt pseudopodia, which are immediately withdrawn, so that no progressive movement results. The cytoplasm appears more refractive than in the vegetative stage, and it is but rarely that any distinction can be made between the ectoplasm and endoplasm, although occasionally the endoplasm appears to be retracted and surrounded by a clear zone representing the ectoplasm. The nucleus is generally visible as a ring-like, refractive body, within which shining granules of chromatin may be observed. At this stage of development the cytoplasm does not contain much extraneous matter and vacuoles are less numerous, and generally entirely absent.

In stained preparations the parasites, in many instances, show but little structure, owing to the intensity with which they take the stain. In well-decolorized preparations, however, the cytoplasm appears granular and more or less reticulated, while the nucleus presents a deeply stained, rather thick nuclear membrane, and a distinct karyosome consisting of a deeply staining, spherical mass of chromatin. I have observed in the karyosome evidences of division as shown by thinning of the chromatin and a partial separation of the karyosome into two oval bodies, united by a dimly stained thread of chromatic substance. I have never seen a precystic *E. coli* with more than one nucleus, although sometimes it has required considerable care to differentiate cysts containing two nuclei from the precystic forms, in cases in which the cyst-wall was poorly defined. I believe that no reproduction occurs during this stage of development, and that the differences in appearance between the vegetative and precystic forms are, in the latter, entirely preparatory to encystment.

Morphology in the Cystic Stage.—The cysts of *E. coli* are characterized by their large size, when compared with *E. histolytica,* and when fully developed contain eight nuclei, although this number may be exceeded, as many as sixteen nuclei having been observed. The cysts are found most frequently in formed stools, although in patients suffering from diarrhea the cysts may sometimes be observed along with vegetative forms. This occurs only where the cycle of development has already reached the cystic stage before the stools became semifluid or fluid.

The living cysts of *E. coli* are spherical or oval in shape and refractive in appearance. The size varies considerably, cysts being observed measuring as much as 25 or 30 microns in diameter, and others as little as 10 microns, but the average diameter is about 15 microns.

The cyst-wall varies much in appearance with the age of the cyst, being barely distinguishable as a delicate line surrounding the organism at the beginning of encystment, but presenting a double outline when the cyst is fully developed, the membrane being of considerable thickness. Just prior to encystment the organism rids itself of any bacteria, crystals or other extraneous matter that it may contain and the cytoplasm assumes a distinctly alveolar appearance. As encystment progresses this alveolar structure is gradually replaced by a finely granular one, and in some of the cysts a large vacuole develops, filling nearly two-thirds of the cyst, the cytoplasm being collected into a granular band surrounding the vacuole, and containing one or two nuclei. When two nuclei are present they are often situated at opposite sides of the cyst, separated by the vacuole already mentioned.

In some of the younger cysts a few shining granules of chromidia may be observed, but these disappear before division of the nucleus begins, and I have never observed any of the large chromidial masses so characteristic of the cysts of *E. histolytica.*

The cysts may contain from one to as many as sixteen nuclei, the normal number, when the cyst is fully developed, being eight. In the living specimen these nuclei appear as ring-like, refractive bodies scattered through the cyst, and, on account of being situated at different levels in the cytoplasm, it is necessary to focus carefully in order to bring them all into view. The cysts that contain more than two nuclei very rarely show the large vacuole mentioned, this being most often observed during the primary division of the nucleus.

In specimens of *E. coli* stained with iron-hematoxylin or chlorid of iron-hematoxylin, the cystic membrane remains unstained, in most instances appearing as a hyaline band, of single or double outline, encircling the cyst. The cytoplasm appears alveolar in the young cysts, but in the older ones it generally is finely granular in appearance. In the cysts showing but one nucleus a large vacuola is often present and this may be found in cysts showing two distinct nuclei; but in the cysts containing from four to eight nuclei I have never observed the vacuole, so that it is evident that it disappears as nuclear division progresses. In the cysts containing the large vacuole, the nucleus, when single, is of large size and presents evidences of division, the karyosome being divided into two oval or spherical portions, connected by strands of chromatin, or entirely divided. In these nuclei the membrane is well stained, of considerable thickness, and not infrequently the nuclear chromatin, instead of being collected into a distinct, dividing karyosome, appears to be divided into threads running from pole to pole of the elongated nucleus. In the cysts containing two nuclei and a large vacuole, the nuclear membrane of each nucleus is distinct, and there may be a well-defined karyosome consisting of a deeply stained mass of chromatin, or evidences of consisting of a deeply stained mass of chromatin, or evidences of division may be noted, the nuclear chromatin being arranged in more or less definite strands within the elongated nucleus. In the cysts that do not present the large vacuole, the nucleus, when single shows a definite karyosome, a well-marked nuclear membrane, and granules of chromatin scattered through it between the membrane and the karyosome. In such cysts the nucleus resembles closely that observed in the vegetative forms. In the cysts that contain two nuclei, however, evidence of division of these is often noted, the nuclei resembling those found in the cysts containing the large vacuole.

As nuclear division progresses in the cysts, the resulting nuclei become much reduced in size, are generally spherical in shape, and the elongation and arrangement of the chromatin into threads stretching from pole to pole is not so evident. In fact, many of these nuclei consist merely of a well-defined nuclear membrane, containing a loose mass of granules near the center, representing the karyosome. In many of them a considerable thickening of the nuclear membrane appears at one portion of the periphery, giving a peculiar cup-shaped appearance to the outline of the membrane.

In the cysts with more than eight nuclei the nuclei are still more reduced in size and consist simply of a thin nuclear membrane containing scattered chromatin granules, or a few granules situated at the center, representing the karyosome.

It is not unusual to observe cysts that are evidently undergoing degeneration, the cystic membrane being poorly defined and the entire cytoplasm of the cyst being filled with deeply stained granules, threads or masses of chromatin, the nucleus having disappeared, or, if present, being distorted in shape, while the nuclear structure is obscured or atypical in character. Sometimes these degenerate cysts contain one or more compact, quite large masses of chromatin, resembling the chromidial masses so characteristic of the cyst of *E. histolytica,* but the absence of a definite nucleus, and the smaller size, and irregular shape of these masses should serve to distinguish the cysts containing them from those of the latter parasite.

Resistance to Physical Conditions and Chemical Agencies.—Practically no work has been done on the resistance of *E. coli* to physical conditions or to chemicals, but reasoning from analogy, it is probable that this species follows very closely *E. histolytica* in this respect.

Relation to Disease.—*E. coli* is frequently observed in the feces in both health and disease, and although it is probably world-wide in its distribution, the percentage of persons infected varies greatly in different localities, being highest in the tropics and subtropics, and lowest in the temperate zones.

This species has been often mistaken for the pathogenic *E. histolytica,* and for this reason it is important to know the percentage of persons that may be expected to show it in various parts of the world. Schaudinn[1] found it present in 50 per cent. of healthy persons in West Prussia; in 20 per cent. in Berlin, and in 66 per cent. of healthy people examined on the shores of the Adriatic Sea. In 1905, I[32] examined over 200 healthy American soldiers at San Francisco, recruited from all parts of the United States, and found that 65 per cent. of them showed *E. coli* in their stools after a dose of magnesium sulphate. Later, in conjunction with Ashburn,[33] I found 71 per cent. of infections with this parasite among 107 soldiers examined at Manila, Philippine Islands. Vedder[45] found 50 per cent. of healthy American soldiers infected in the Philippines, and 75 per cent. of the native troops. Vedder's observations were made on 50 American soldiers and the same number of Philippine scouts. Sistrunk[35] found *E. coli* in eleven out of 145 patients examined at St. Mary's Hospital, Rochester, Minn., the patients suffering from diseases other than dysentery, while Rosenberger,[36] at the Philadelphia General Hospital, found 105 out of 106 insane patients examined infected with this parasite. In 1905, I[37] examined the stools of 250 patients suffering from diseases other than dysentery, at the U. S. Army General Hospital in San Francisco, and found that 49 per cent. of them showed *E. coli* in their feces.

From these data it is evident how widespread is infection with this parasite, and in what a large proportion of persons in both health and disease it may be demonstrated. It is also evident that if one were to rely only on the presence of an entameba in the feces in the diagnosis of dysentery, without reference to the species present, every one of these persons would have been diagnosed as suffering from a latent entamebic dysentery, and this was exactly what was done prior to the work of Schaudinn and his followers.

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[32] Craig, Charles F.: Observations Upon Amebas Infecting the Human Intestine, Am. Med., 1905, ix, 854, 897 and 937.

[33] Ashburn, P. M., and Craig, C. F.: The Work of the Army Board for the Study of Tropical Diseases in the Philippine Islands, Mil. Surg., 1907, xxi, 38, 140, 220, 336 and 527.

[34] Vedder, E. B.: An Examination of the Stools of One Hundred Healthy Individuals with Special Reference to the Presence of Entamoeba Coli., Jour. Am. Med. Assn., 1906, xlvi, 870.

[35] Sistrunk, W. E.: Intestinal Parasites Found in Individuals Residing in the Northwest, Jour. Am. Med. Assn., 1911, lvii, 1507.

[36] Rosenberger, R. C.: Proc. Path. Soc., Philadelphia, 1912, v, 27.

[37] Craig, Charles F.: Observation Upon Amebas Infecting the Human Intestine. Am. Med., 1905, ix (reference 103); also The Parasitic Amoebae of Man, Philadelphia, 1911.

It is also evident that the question of the pathogenicity of *E. coli* becomes a most important one, and it has been absolutely proved that this species of entameba is harmless. While much work was accomplished prior to Schaudinn's researches, and there was a well-grounded belief that certain species of entamebas were non-pathogenic, it was not until Schaudinn's paper appeared that there were sufficient data to enable one to differentiate the species of entamebas. Schaudinn proved on his own person that *E. coli* is a harmless parasite, capable of living in the intestine, but incapable of penetrating the mucous membrane or causing the lesions or symptoms of dysentery.

In 1905, while studying entamebas at the Army General Hospital, in San Francisco, I tried repeatedly to produce dysentery in young kittens with *E. coli,* both by injecting into the rectum material containing entamebas and by feeding similar material containing both the vegetative and encysted forms, but I was never able to produce the least symptom of dysentery, although my experiments with material containing *E. histolytica* were successful. My experiments were confirmed by numerous investigators and the recent contribution of Walker and Sellards[21] furnishes the final proof of the harmless nature of this parasite.

These investigators fed twenty men with material containing the cysts of *E. coli,* of which number seventeen became parasitized at the first feeding. None of these men developed dysentery, although Walker and Sellards were successful in producing dysentery in some of the men to whom they fed material containing *E. histolytica.* The period of incubation varied from one to eleven days in the case of *E. coli,* with an average of 4.7 days.

This parasite may persist in the intestine of man for a very long period of time, and I have personal knowledge of infections with *E. coli* that have lasted for from three to ten years, during which time no symptoms of dysentery have ever developed.

Differential Diagnosis.—Owing to the large proportion of infection with *E. coli* in regions where entamebic dysentery occurs, and the ease with which this species may be confused with the pathogenic *E. histolytica.* it is most important that the two species be differentiated. This may be best done in the living condition, from a practical point of view, but such a diagnosis should, if possible, be confirmed by preparations wet-fixed and stained by one of the hematoxylin methods, preferably Heidenhain's or Mallory's iron-hematoxylin method.

In the vegetative stage of development, in living preparations, *E. coli* may be differentiated from *E. histolytica* by its sluggish motility, poor distinction between the ectoplasm and endoplasm, large, clearly visible nucleus, and the absence of red blood-corpuscles within the endoplasm, when the stools contain blood. In stained preparations, in this stage of development, the parasite is distinguished from *E. histolytica* by the thick nuclear membrane, large granules and clumps of chromatin on the inner side of the nuclear membrane, the large, compact karyosome, and the absence of red blood-corpuscles within the endoplasm. In the precystic stage of development, in both living and stained preparations, it is exceedingly difficult and often impossible to differentiate this species from *E. histolytica,* but there are almost always vegetative or cystic forms present on which such a differentiation may be based.

In the cystic stage of development, *E. coli* may be differentiated from *E. histolytica,* in the living condition by the large size of the cyst, its thicker wall, the absence of large chromidial bodies within it, and the presence of eight or more nuclei, only four nuclei being present in the cyst of *E. histolytica.* The same differential points are of value in the stained preparations.

OBSERVATIONS ON CRAIGIA HOMINIS, CRAIG, 1906, EMEND. CALKINS, 1912

In 1906, I observed this organism in the feces of a Filipino suffering from chronic diarrhea, and the same parasite was afterwards observed in the feces of five other Filipinos. I published my observations in the same year,[38] giving the parasite the name *Paramoeba hominis,* placing it in the genus *Paramoeba* founded by Schaudinn to include a marine ameba, because of its general resemblance to *P. eilhardi,* the type-species of the genus. Doflein,[39] suggested that this parasite should be placed in a new genus, as he did not consider that it was a true parameba and, in 1912, Calkins[9] established for it the genus *Craigia.*

Regarding the parasite Calkins says:

> Craig, 1906, observed a small amoeba in the human intestine in six cases of chronic diarrhoea. He named it *Paramoeba hominis* because of the presence of an accessory body which he compared with the *Nebenkörper* of *Paramoeba eilhardi* and the formation of flagellated swarmers. The identity of the accessory body with the Nebenkörper is questionable while the single flagellum of the swarmers is sufficient to throw it out of the genus named by Schaudinn. For these reasons I propose to give a new generic name —*Craigia*—after its discoverer.

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[38] Craig, Charles F.: A New Intestinal Parasite of Man, Am. Jour. Med. Sc., n. s., 1906, cxxxii, 214; also "The Parasitic Amoebae of Man," Philadelphia, 1911, p. 215.

[39] Doflein, F.: Lehrbuch der Protozoenkunde, Ed. 3, 1911, p. 603.

Further study of this parasite has convinced me that Professor Calkins' criticisms regarding the generic position are just, and I am in agreement with him that it should be placed in a new genus.

But very little is known regarding the distribution of this parasite. At the time that I described it I had not encountered any infections except in native Filipinos, but in 1908, at Fort Leavenworth, I observed three infections with the organism in American soldiers who had recently returned from the Philippine Islands. During the past four years I have been so situated that I have had no opportunity of continuing observations on the parasite, but recently I have been informed by Dr. W. D. Bretz that he has observed a case of infection at Memphis, Tenn., so that it is evident that the parasite also occurs in the United States. Indeed, I have always been convinced that a careful study of the feces in cases of chronic diarrhea would demonstrate that *C. hominis* has a wide distribution and is a comparatively common parasite, being mistaken in its ameboid stage of development for *E. coli,* and in its flagellate stage for trichomonads or cercomonads.

Morphology.—C. hominis passes through both an amebic and a flagellate stage of development, and it is quite easy to follow the entire life cycle by making frequent examinations of the feces from day to day, while the symptoms of diarrhea are present. There are still certain points regarding the various phases of the cycle that are undiscovered or undecided, but I have been able to study each stage of development, including encystment, the formation of the swarmers, the process of longitudinal division of the flagellates, and the development of the amebic from the flagellate stage. During each of these phases of development the morphology of the parasite varies so that it is necessary to consider each separately in our description.

The life cycle of the organism may be briefly described as follows: Beginning with the amebic stage, the parasite reproduces by simple division for a number of generations (as long as conditions are favorable) as a typical ameba, at the end of which time it encysts, and within the cyst there develop numerous small swarmers, which finally escape, develop each a single flagellum, and reproduce by longitudinal division for several generations, after which the flagellum disappears, the organism develops ameboid motion, and again begins the amebic stage of development.

For convenience of description the morphology in the amebic stage, the cystic stage and the flagellate stage of development will be considered separately.

Morphology in Amebic Stage.—The living parasite varies considerably in size in this stage of development, organisms measuring as little as 10 microns being sometimes observed, while others measure as much as 25 microns in diameter; but the average measurement in diameter at this stage is about 18 microns. The resting amebas are round or oval, but when moving they are very irregular, and several pseudopodia may be projected from the periphery at the same time. Motility in the fully developed amebas is very active, progressive movement is well marked, and there is a sharp distinction between the ectoplasm and endoplasm, the latter being much more refractive, the ectoplasm being thin and veil-like in appearance. In the motionless organism there is no distinction between the ectoplasm and endoplasm, and this is also true of the smaller parasites, in which the motility is very sluggish. In the living organisms a nucleus can nearly always be distinguished appearing as a refractive, spherical body, surrounded by a thick and more refractive nuclear membrane of granular consistence. Often this membrane appears to be composed of refractile rods arranged end to end around the periphery of the nuclear substance. In some of the fully grown amebic forms a brightly glistening oval body, minute in size, may be observed lying near or in contact with the nucleus, appearing much like the blepharoplast of a trypanosome or of the flagellate stage of a Leishmania. This is the body that, in my original description, I considered corresponded to the *Nebenkörper* of *Paramoeba eilhardi,* as described by Schaudinn.

The ectoplasm is always to be distinguished from the endoplasm in the larger organisms when the parasites are in motion, but when motility is very sluggish in the smallest parasites the distinction is lost, although even in the smallest examples of *C. hominis* the ectoplasm is well defined if motility is at all active. The ectoplasm appears homogeneous, while the endoplasm is reticular in structure, often giving the appearance of being filled with vacuoles, and it may contain bacteria, crystals and red blood-corpuscles. I have not observed vacuoles in the cytoplasm of this species but have no doubt that under favorable conditions they do occur.

In stained preparations the ectoplasm and endoplasm are not differentiated, the cytoplasm appearing reticulated and containing bacteria, crystals, and red blood-cells in many instances. The nucleus stains intensely, the nuclear membrane being thick and well defined, while the karyosome is large, and separated from the nuclear membrane by an unstained area devoid of chromatin. The karyosome stains uniformly throughout, a centriole being absent. The nuclear morphology is very similar to that of the genus *Vahlkampfia,* the only difference so far as I have been able to observe, being that this species has a smaller karyosome.

The accessory nuclear body is found only in some of the larger organisms. It appears as a deep black dot or thick, oval rod, lying near or almost in contact with the nucleus.

Organisms undergoing division are observed in stained preparations, and it is apparent the division first occurs in the accessory body, for this body may be seen divided before complete division of the nucleus has occurred. During division the chromatin of the nucleus becomes arranged in strands running from pole to pole of the elongated nucleus, and in some instances traces of an equatorial plate may be observed. Often the chromatin is collected into two cup-shaped masses at the poles of the nucleus and the space between is filled with fine granules without any definite arrangement. Organisms are observed containing two distinct nuclei, each possessing the structure found in the nucleus of adult *Craigia* before division. I have never observed any evidences of schizogony in this species.

Morphology in the Cystic Stage.—When alive the cysts of *C. hominis* are slightly smaller than the adult vegetative forms, measuring, on the average, about 15 microns in diameter, but there is a well-marked precystic stage, in which ameboid motility is lost, the organisms contract and expel any extraneous matter that they may contain, and then begin to rotate rapidly without changing position in the material containing them. This process of rotation may last for as long as one hour, but generally ceases in about fifteen minutes, when it will be noted that a distinct cyst-wall has been formed, possessing a double outline, while the nucleus and accessory body may still be differentiated within the cytoplasm. As development progresses the nucleus and accessory body disappear and the cyst becomes filled with refractive, spherical granules, which eventually become the young flagellates. When fully developed, the cysts of *Craigia hominis* appear as refractive, spherical bodies, surrounded by a well-defined cyst-wall, and containing numerous very refractive spherical bodies.

The cysts stain so intensely, evidently because of the richness of chromatin, that it is impossible to make out much in the way of morphology in such specimens. In specimens that have been decolorized for a long time one may sometimes see a collection of small ring-like bodies, evidently representing the nuclei of the swarmers, but no fine morphological details can be distinguished.

Morphology in the Flagellate Stage.—I have never observed the actual liberation of the flagellates from the cyst, but groups of these organisms are observed arranged in a spherical mass, and surrounded by granular detritus, evidently the remains of the cyst.

The young flagellates appear at first as spherical bodies, measuring from 3 to 6 microns in diameter, having a finely granular cytoplasm, and a poorly defined refractive nucleus. If these young forms be watched a single, very delicate flagellum appears at one portion of the periphery, and as soon as this occurs, the organism moves forward in a jerky manner, propelled by the flagellum. Contrary to my original belief that the flagellum is situated posteriorly, I now believe it is situated anteriorly, for motion is observed in both directions, and in the fully developed flagellate motion is more often observed in the direction of the flagellum.

When fully developed the flagellates measure from 10 to 20 microns in diameter, are spherical in shape, slightly elongated at the portion from which springs the flagellum, and composed of a finely granular cytoplasm in which lies a small, but well-defined nucleus. In some of the flagellates the accessory nuclear body may be distinguished as a brightly refractive dot or rod near the nucleus. The latter is spherical in shape and has a well-defined, delicate nuclear membrane composed of refractile granules.

Reproduction in this stage of development occurs by longtiudinal division, and organisms are observed in which every stage of this process may be demonstrated. I have not been able to ascertain if the accessory nuclear body divides before the nucleus does, but parasites are observed containing two accessory bodies, two nuclei, and showing commencement of division in the flagellum, while others are observed in which the division of the two flagellates is almost complete, including the flagellum.

In stained preparations the cytoplasm of the flagellates stains very intensely and it is difficult to make out the structural details of the nucleus. The nuclear membrane is thinner than in the amebic stage of existence, and is apparently composed of minute granules; the karyosome is comparatively large and is surrounded by an unstained area as in the vegetative forms. In fact, the nucleus in the flagellate organisms is quite similar to that in the vegetative stage and markedly resembles that of the genus *Vahlkampfia*. The accessory nuclear body stains as a black dot or rod. The flagellum stains poorly; the most careful focusing is required to demonstrate it in most organisms. In the dividing forms two accessory nuclear bodies may sometimes be distinguished, while the nucleus shows evidences of a primitive form of mitosis, the karyosome dividing and the chromatin collecting at the poles of the elongated nucleus.

Relation to Disease.—There is no evidence that *Craigia hominis* is a pathogenic parasite, beyond the fact that I have found it present only in patients suffering from diarrhea, and that treatment causing it to disappear also resulted in the cure of the disease. I have been unable to produce infection in kittens with material containing this parasite, and there are no reports of pathologic lesions caused by it, so that at present, while I am of the opinion that it is capable of causing a form of chronic diarrhea, its pathogenicity is still unproved.

Differential Diagnosis.—In my original contribution I called attention to the likelihood of confusing this parasite with other entamebas and with trichomonads and cercomonads, and described in detail the differential points, but despite this, Hartmann[40] has suggested that I mistook certain stages in the development of *E. coli* and *Trichomonas intestinalis* for a new species of intestinal entameba. The absurdity of such a statement must be apparent to any one who has studied the organisms mentioned, and it may be stated that only one entirely inexperienced in the study of the protozoa of the intestine could make such a mistake.

C. hominis is distinguished from either *E. histolytica* or *E. coli* by its small size, the character of the nucleus, the presence of an accessory nuclear body, the structure of the cysts, and the production of swarmers within the cysts. From *T. intestinalis* it is distinguished in the flagellate stage by its larger size, the absence of an undulating membrane, the single flagellum, and the spherical shape. In the amebic stage it is distinguished from the resting forms of *T. intestinalis,* which sometimes possess a very limited degree of ameboid motion, by the larger size and the active progressive motion, which is never observed in trichomonads.

The differential points mentioned also serve to distinguish *C. hominis* from any entameba or intestinal flagellate hitherto described.

It is probable that careful observation will demonstrate that many of the instances of chronic diarrhea now accredited to *T. intestinalis* are really due to this parasite, but this will not be determined until there is a more general resort to the microscopical examination of the feces in clinical diagnosis.

OBSERVATIONS ON VAHLKAMPFIA LOBOSPINOSA, CRAIG, 1912, EMEND. 1913

The free-living amebas belonging to the genus *Vahlkampfia* are of great interest because of their frequent occurrence in material from cases of entamebic dysentery and the fact that they can be easily cultivated on various culture mediums. The genus also contains parasitic species found in some of the lower animals, and Wenyon,[41] Chatton,[6] James[42] and others have observed vegetative forms of *Vahlkampfia* in feces from the human intestine, so that it appears to be proved that some species of this genus are able to live a parasitic existence in man, but in every instance these organisms were easily distinguished from *E. histolytica* and *E. coli* and presented the typical limax structure ordinarily observed in cultures.

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[40] Hartmann, M.: Article on "Die Dysenterie Amoeben," in von Prowazek's Handbuch d. Path. Protozoen, 1912, i, 51.

[41] Wenyon, C. M.: Intestinal Amebiasis, Brit. Med. Jour., 1913, 2495, p. 1244.

[42] James, W. M.: Personal communication.

As these amebas occur so frequently in cultures made from feces or material from liver abscesses in cases of entamebic dysentery, almost always as contaminations, the morphology of a typical example of the genus will be described. This organism, which I named *Amoeba lobospinosa* in 1912,[43] but which really belongs to the genus *Vahlkampfia*—and for which I now suggest the name *Vahlkampfia lobospinosa*—has a most interesting history. It was originally cultivated from the feces of a patient with entamebic dysentery by Dr. Musgrave, in Manila, who described it as Ameba 11524 of his series. The culture with which I have worked is descended from a culture he sent to the Army Medical Museum in 1905. I have also worked, so far as morphology and life history is concerned, with two other cultures of the same organism, which were sent to the museum by the Board for the Study of Tropical Diseases, in Manila, in 1908. This organism has thus been cultivated on Musgrave and Clegg's agar-medium for a period of nearly eight years, and during this time the morphology has not changed, but has remained that of a typical *Vahlkampfia*. In a recent contribution Calkins and Williams[5] have shown that on certain mediums this organism changes considerably in morphology and closely resembles, as they claim, *E. histolytica* or *E. coli*, and their work will be referred to later.

On the medium of Musgrave and Clegg, *Vahlkampfia lobospinosa* presents two well-defined stages of development, the vegetative and the cystic, and the morphology of the organism varies in each stage.

Morphology in Vegetative Stage.—The size of the organism varies exceedingly, measurements of from 8 to 25 microns in diameter being frequently observed, but the average diameter is about 16 microns. The shape, when motionless, is oval or spherical, but when moving the organisms are very irregular in shape. Motility is sluggish and progressive motion not very marked; the pseudopodia are of two varieties—short and blunt, and longer and spinose. The lobose pseudopodia are present when the organisms are actively motile, but the spinose pseudopodia are more frequently observed when motility is absent or very sluggish. The spinose pseudopodia are extruded from the periphery of the ameba very rapidly and as rapidly withdrawn, so that it is often difficult to distinguish them. Both lobose and spinose pseudopodia may be present at the same time.

The nucleus is well defined, appearing in the living organism as a spherical, refractive mass surrounded by a narrow hyaline area, while the nuclear membrane is indistinct. In most of the vegetative forms a single, contractile vacuole is present, which contracts once in about fifteen seconds, and which, when most clearly defined, is situated near the nucleus but travels toward the periphery before it contracts. In most of the organisms the contractile vacuole appears to be situated at the periphery when contraction occurs.

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[43] Craig, Charles F.: Observations Upon the Morphology of Parasitic and Cultural Amoebae, Jour. Med. Research, 1912, xxi, 1.

In stained specimens the distinction between the ectoplasm and endoplasm, which is quite marked in the living condition, is lost, and the entire cytoplasm stains a brownish gray or gray, appears reticular in structure, and composed of granular material. The nucleus is characteristic in structure, being composed of a large karyosome, filling at least two-thirds of the entire nucleus, surrounded by a clear unstained area, which, in turn, is surrounded by a zone of fine chromatin granules forming a poorly stained nuclear membrane. The karyosome stains intensely and, unless the preparations are well differentiated, does not show a centriole, but in well-stained and decolorized preparations a centriole may be observed within the karyosome, consisting of one or two almost black dots. The unstained area surrounding the karyosome is devoid of chromatin granules and no traces of a linin network can be distinguished in this area. In many of the vegetative forms the nuclear membrane cannot be distinguished from the cytoplasm, but it may appear well stained and then consists of a rather thick membrane, on the inner side of which there is a zone of fine chromatin granules.

The cytoplasm contains many bacteria and often the single vacuole is well differentiated, together with unstained areas demonstrating the reticular nature of the protoplasm.

During the vegetative stage of development reproduction occurs by simple division, the nucleus often showing well-defined mitotic figures. Organisms are observed in which the karyosome as well as the entire nucleus is greatly lengthened, while evidences of division of the centriole are noted in well-differentiated preparations. A later stage in division is shown in organisms having deeply stained crescentic bodies at each pole of the nucleus, connected by fine filaments of poorly stained material, the whole forming a well-defined spindle. An equatorial plate is not infrequently observed consisting of a band of deeply stained granules of chromatin stretching across the spindle midway between the polar bodies, and sometimes a distinct division of this plate into two rows of deeply stained granules may be observed. Still later the equatorial plate and the spindle disappear and the nucleus is divided into two portions, spherical in shape, each having a distinct karyosome and a poorly defined nuclear membrane. In this species the mitotic character of the division of the nucleus is well marked, much more so than it is in the intestinal entamebas.

Morphology in the Cystic Stage.—Vahlkampfia lobospinosa produces cysts whenever the cultural conditions are unfavorable to vegetative existence, and on the ordinary culture mediums the cysts are characteristic of this genus, only one daughter ameba being formed in each cyst. In size the cysts vary from 8 to 15 microns in diameter, the average being about 10 microns. The youngest cysts, when living, have a delicate cyst wall, of single outline, but the fully developed cysts show a thick wall, very refractive in character, and having a well-marked double outline. The cysts are spherical in shape so long as the medium is moist, but as drying occurs they contract unequally and irregular forms are produced, generally quadrilateral or pyramidal in shape. The old cysts often have a very thick wall which appears cracked or folded over in places, thus giving the cyst a very characteristic appearance. The cytoplasm of the young cysts appears finely granular but free from bacteria, and the single nucleus may be observed near the center of the cyst. In the older, living cysts the nucleus is often invisible and the cyst appears to be filled with minute refractive granules, the nature of which I have been unable to determine.

In stained preparations the cytoplasm appears granular and the nucleus presents the same structure that is observed in the vegetative forms before division occurs. I have never observed more than one nucleus in a cyst, nor have I ever observed any evidences of division of this nucleus, so that encystment in this species, so far as it is shown on ordinary culture mediums, is purely a protective process, as reproduction does not occur within the cyst.

In brief, the description given above answers to the appearance of *V. lobospinosa* as observed in cultures on Musgrave and Clegg's nutrient agar, but the recent work of Williams and Calkins[6] has shown that when this species is grown in pure culture on brain-tissue medium very marked variation occurs in its morphology from what occurs when it is grown, in conjunction with bacteria, on ordinary mediums. They have found that the contractile vacuole disappears from the vegetative forms, the nuclei resemble in structure the nuclei of the entamebas, and the cysts become multinucleate, from two to four nuclei being present in many of them. Williams and Calkins consider these variations as significant of the parasitic nature of the species, but are very conservative regarding their exact significance, saying:[6] "We do not wish, however, to lay too much stress upon these experimental results; conditions of the culture might be such as to bring about variations when these do not occur under conditions 'normal' to the organism." These observations are of the utmost interest as showing how profoundly a protozoan organism may be modified by unnatural cultural conditions, but there is no reason to believe that these modifications in any way connect this typical free-living ameba with the entameba of the intestine, as *E. histolytica* or *E. coli,* for even though the structure of the nucleus is modified it is perfectly evident to anyone who has worked with the entamebas that none of the photomicrographs published with the paper of Williams and Calkins show amebas with a nucleus in the least like the nucleus of either *histolytica* or *coli,* while even in the drawn plate the nuclei are markedly dissimilar in most of the drawings. It is a fact that whenever a *Vahlkampfia* has been found parasitic in the human intestine, and this has occurred in a few cases, as mentioned, the morphology has been typical of the limax type of ameba and the forms observed by these authors have never been noted. As regards the relation of these free-living species to disease the observations of Walker and Sellards, hereafter considered, are conclusive.

Relation to Disease.—There is at present no evidence that any species belonging to the genus *Vahlkampfia* is capable of producing disease in man, and it is evident from the investigations of many authorities that, in most instances, the species of this genus are actually incapable of establishing themselves as parasites in man. They are all essentially free-living amebas, so far as their relation to man is concerned, and while a very few instances have been reported of infection with the vegetative forms of *Vahlkampfia*, the infection lasted but a short time and no symptoms or lesions were produced by the organism. Therefore, we are justified in believing that such instances are accidental, and while they may be interesting from the point of view of the evolution of parasitism in a species, at present they possess no practical importance to the clinician.

To consider all of the observations that go to prove the fact that the species of the genus *Vahlkampfia* are essentially free-living as regards their relation to man would be only to repeat, but the recent work of Walker and Sellards, in my opinion, proves conclusively that the ordinary cultural amebas bear no relation whatever to the intestinal entamebas, but are in nature free-living and incapable of existing as parasites in man.

Walker and Sellards[21] experimented on ten men by feeding them cultures representing thirteen different strains and eight species of free-living amebas isolated from the Manila water-supply and other nonparasitic sources, from the stools of healthy persons and persons suffering from diseases other than dysentery, and also from dysenteric stools. They found that when cultures of these amebas were ingested by the men the amebas could be recovered from their stools in culture during the first few days after feeding but not subsequently, and that the microscopical examination of such stools always resulted negatively. No symptoms of dysentery occurred in any of the men, although they were observed for months, and as the result of their work the authors draw the following conclusions:

> 1. The cultivable amoebae are incapable of living parasitically in the intestinal tract of man.
>
> 2. The amoebae, when obtained in cultures from stools, intestinal contents, or liver-abscess pus, are derived either from cultural contaminations or from encysted amoebae which have been ingested with water or food and have passed unchanged through the intestinal tract.
>
> 3. The cultivable amoebae are non-pathogenic, and consequently play no rôle in the etiology of endemic tropical dysentery.

In the light of these conclusive experiments it is very evident that no amount of evidence based on mere changes in morphology or life cycle produced by growing free-living amebas on unnatural culture material can be considered as of the slightest value in connecting them with the true entamebas, but that at most these variations simply indicate the path by which the present species of entamebas reached their parasitic mode of existence. From the point of view of evolution the experiments of Williams and Calkins are most valuable and interesting, but they in no wise affect the present classification of the parasitic species. I believe that it is proved that the cultivable amebas cannot, in the vast majority of instances and under natural conditions, live as parasites in man, and that they are entirely distinct from the entamebas and bear no relation to the etiology of entamebic dysentery.

In conclusion I desire to state that the personal observations recorded in this contribution were made at the U. S. Army General Hospital, San Francisco, Cal.; the Division Hospital, Manila, P.I., while the writer was a member of the U. S. Army Board for the Study of Tropical Diseases in the Philippines; the Rockefeller Institute for Medical Research, New York; the Laboratory of the Army Medical School, Washington, D.C.; and the Department Laboratory, Central Department, U. S. Army, at Fort Leavenworth, Kansas. For the photomicrographs, of which Figs. 1 and 2 are reproductions, I am indebted to Capt. Arthur C. Christy, U. S. Army. They were made from preparations stained with iron-hematoxylin and fixed with Schaudinn's sublimate alcohol solution.

THE PHYSIOLOGIC DEGENERATION OF THE MESONEPHROS

WITH A CONSIDERATION OF ANTAGONISTIC ACTION OF ORGANS AND OF FUNCTIONAL MUTATION WITH MORPHOLOGICAL PERSISTENCE *

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I propose to draw attention to certain embryological processes and phenomena which appear to have escaped a more than cursory attention by the pathologist and, if a perusal of the literature and an inquiry among those able to judge lead me to suppose correctly, have received a rather inadequate consideration by anatomists and physiologists. The road, therefore, is difficult to travel, and the observations and considerations which are recorded below will appear necessarily fragmentary and incomplete. Indeed, the difficulty of obtaining suitable material and other more personal obstacles allow me to offer no more than an outline of the matter. That, however, seems warranted by the importance and the unfortunate neglect of the subject. Even in incomplete form it may, nevertheless, obtain the interest and future help of those who by position and experience are able to enlarge on the facts and elaborate the conclusions to be drawn therefrom.

Perhaps it may not be amiss to review briefly, as an introduction, our present knowledge and ideas regarding renal development in general and the mesonephros in particular.

I. INTRODUCTORY GENERAL PART[1]

It is of course impossible to present within the scope of this paper, which proposes to deal only with certain phases of nephric development, a thorough discussion of the whole complex and still disputable subject of the origin of the excretory system and the relations it may have to the original annelid nephric organ. These to the pathologist by no means unimportant questions, must be studied elsewhere.[2] I shall con-

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[1] The introductory general part was essentially written for those unacquainted with present views of renal development and of the position and structure of the mesonephros; others may turn immediately to the second special part.

[2] Consult Felix, W.: The Development of the Urogenital Oragns, in Man-

fine myself to a sketch of those features a knowledge of which appears necessary for an intelligent understanding of the subject at issue.

The kidney of all amniotes discloses, as is well known, its phylogenetic travels much plainer than any other organ. By succession and partly coexistence appear three distinct excretory organs, pronephros, mesonephros and metanephros. The pronephros disappears rapidly, but the mesonephros, or wolffian body, acquires full development and a high degree of differentiation. In man, particularly, this rises to a better state of evolution than in some of the lower animals, in pigs it reaches an enormous size and recedes only in embryos of 10 cm., while in reptiles it continues through part of the postnatal life. Thus in lizards the mesonephros persists to the end of the first year and, according to Braun,[3] retrogression of the mesonephros does not commence until after the first hibernation. On the other hand, it happens that in the mouse the wolffian body develops only incompletely and is even devoid of all glomeruli.

It is, therefore, evident from the start that the development of the amniotic kidney is quite unlike the gradual, uniform development of other organs, but *serial,* for it appears that pronephros, mesonephros and metanephros are to a considerable extent at least independent organs, which take origin from closely adjoining and partly overlapping segments of the mesoderm, so that the pronephros develops most cranially, caudally to it the mesonephros and still more caudally the metanephros or permanent kidney. The exact genetic relation of these three organs has been, and still partly is, a disputed question. For our discussion it is sufficient to emphasize that a relation exists so far as they represent renal excretory organs patterned on one structural scheme, but of a growing complexity which is demanded by progressively higher grades of general development, and corresponds to various stages of animal evolution. As one is replaced by the other the predecessor appears thereafter by recapitulation, rudimentary or provisional. A certain

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ual of Embryology, edited by F. Keibel and F. P. Mall, Philadelphia and London, J. B. Lippincott Company, 1912.

Felix, W.: Die Entwicklung des Harnapparats (1904), in Hertwig's Handbuch der vergleichenden Entwicklungslehre der Wirbelthiere, Jena, G. Fischer, 1906.

Gaskell, W. H.: The Origin of Vertebrates, London, etc., Longmans, Green & Co., 1908.

Broman, Ivar: Normale und abnormale Entwicklung des Menschen, Wiesbaden, Bergmann, 1911.

Bonnet, R.: Lehrbuch der Entwicklungsgeschichte, Berlin, Paul Parey, 1907.

[3] Braun: Das Urogenitalsystem der einheimischen Reptilien, Arbeiten aus dem zool.-zoot. Institut zu Würzburg, 1877, iv.

Schreiner, K. E.: Ueber die Entwicklung der Amnioten Niere, Ztschr. f. wissensch. Zool., 1902, lxxi, 1-189.

structural resemblance may, therefore, be noted in all three which in amniotes is necessarily closest between mesonephros and metanephros. In myxinoids the pronephros represents the permanent kidney. In fishes and amphibia it atrophies and is replaced by the better-organized mesonephros. Finally, in amniotes the mesonephros also undergoes retrogression and is replaced by the most highly organized metanephros as permanent kidney. One other and more special relation between these three organs must be noted: There is developed in connection with the pronephros an excretory duct, called the primary excretory or segmental duct, which takes origin from the thirteenth and fourteenth and possibly other caudal segments of the pronephric anlage. It penetrates early into the cloaca. From it descend directly the wolffian duct of the mesonephros and the ureter of the metanephros with their derivatives.

An understanding of the functional and structural characteristics of all three kidneys is much helped by tracing them through phylogenetic evolution. In the lowest unicellular forms of animal life the general surface of the cell serves as a medium for the discharge of waste products. But under certain conditions, probably increased energy, there appear contracting vacuoles in addition to others of alimentation and distribution. The contracting vacuoles have been regarded as the first evidences of an excretory system. Thus Rhumbler believes that certain excretory granules and crystalline enclosures which were first observed by Stein in 1859, and later thoroughly investigated by Bütschli, are discharged by pulsating vacuoles. The nature of these granules or crystals is held to be either uric acid (Griffiths, 1889) or an oxalate (Bütschli) or calcium phosphate (Schewiakoff).[4]

We see further in the lower metazoa, such as the turbellarins, a complex system of tubes which ramify in the tissues of the body and constitute an independent excretory organ.

The appearance of the coelom or body cavity marks the beginning of a definitely recognizable excretory system which was combined in all probability from the start, or at least very early, with the sexual apparatus. This combination persists to the human organism, in which a separation of urinary and sexual organs has only partly been accomplished. Both form a unit during human embryonic and fetal life, and even in the adult one channel serves both as terminal passage. At the earliest stages of evolution both were represented by the coelom walls which possessed the ability not only of elimination, but also of producing sexual cells, gonads (Gegenbaur[5]). Gradually the coelom developed ducts for conveyance of the excretory products to the exterior. It is very probable that later a certain portion of the coelom wall became reserved for the sexual function and another for the excretory function.

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[4] Von Fürth, O.: Vergleichende chemische Physiologie der niederen Thiere, Jena, G. Fischer, 1903.

[5] Gegenbaur, C.: Vergleichende Anatomie der Wirbelthiere, Leipsic, W. Engelmann, 1898.

Thus originated sexual glands and pronephros, the first definite excretory organ of vertebrates. Notwithstanding their appearance, the association of the two systems continues quite intimate throughout the whole series of vertebrates, and is necessarily most marked during early life.

In this persistent and peculiarly characteristic interchanging relationship of excretory and sexual apparatus rest, as will appear, important factors which seem to enter into the developmental fate of both.

It has been stated that the structural organization of the three excretory glands is based on one scheme. This is dictated by their two main functions. These are (if we neglect for the time certain metabolic activities which acquire importance only in higher animals):

1. To remove useless or dangerous metabolic or foreign substances from the body (excretion).
2. To allow permeation and elimination of superfluous water from the body fluids (filtration).

Both combined maintain constancy in the composition of the body-fluids and the blood. It is very probable that the most primitive urinary organ, the coelom, or body cavity, was able to carry on both functions. Each coelom cell possessed excretory activity, and the coelom wall as a whole formed a membrane permeable for water. With growing complexity of differentiation it became necessary to specialize these functions in particular parts of the coelom cavity. Consequently that portion of the coelom wall which was richly provided with blood-vessels assumed filtrative function by the formation of the external glomerulus. This consisted only of an invagination of blood-vessels into the body cavity. On the other hand, the transverse ducts remained reserved for the more specific excretory function. This constituted the pronephric period. During later stages of development the filtration apparatus of the external glomerulus, originally quite independent, was incorporated in the kidney and quantitatively modified to adapt itself to the new environment and demands. Thus originated the malpighian corpuscles of the mesonephros and later of the metanephros. This union created an organ which again combined, as did the coelom, filtrative with excretory functions, but in a much higher degree of efficiency. At this point all communication between kidney tubules and coelom disappeared, and the latter retained only the mechanical function of separating movable organs from each other and the body walls.

The fact that the kidney of higher animals represents a union of originally independent units is of some interest in relation to its functional activities, for it is likely that both units have largely retained their chief original purposes, the one of filtration, the other of secretion and excretion. In this connection it is interesting to recall that with progressing evolution the tubular secretory structures become not only more numerous but also more complex, and that their cells undergo various processes of differentiation. They show, therefore, important qualitative tissue changes. It is different with the glomerulus. From the one external glomerulus a step to many is made in the mesonephros and a further step to a still greater number in the metanephros. But the glomerular structure, unlike the tubules, remains essentially the same throughout evolution. One would conclude that glomerular function, although quantitatively enormously increased, has not undergone marked qualitative changes.

To recapitulate and sum up: All three kidneys are evolutionary stages of an organ series. They have in common secretory tubules opening into an excretory duct, but their structures arise from different segmental portions of the mesodermal plate, and, therefore, are not identical or evolutionary periods of one organ. At first, during the period of tubular formation from the cranial segments, the tubules are simple and retain segmental arrangement. A glomerulus lies outside and independent to the secretory portion (pronephros). Later, when formed in the dorsal and lumbar regions, tubules appear in greater number and become more complex, and glomeruli appear and are incorporated and connected to the tubules in a fully developed renal organ (mesonephros). In the last stage of sacral development the tubules assume greater complexity and number with a corresponding increase of glomeruli, and they first group themselves around and then unite with an outgrowth from the wolffian duct the ureter and its derivatives, all of which are the direct descendants of the pronephric primary excretory duct (metanephros).

This short, rather crude sketch may perhaps suffice to recall to mind the position which the mesonephros occupies in genetic and individual history, and we may now briefly review its structure and organization.

Attention has been drawn to the fact that the mesonephric tubules develop from those stalks of the primitive mesodermal segments which lie caudally from the pronephros. In mammals these form early a blastema or cell cord which gives rise in its cranial portion to the parenchyma of the mesonephros and later in its caudal portion to the parenchyma of the metanephros. This blastema is commonly spoken of as the nephrogenic cord, and its appearance terminates the existence of the critical period of individual segment stalks and inaugurates the possibility of a greater number of tubules of growing complexity. These tubules empty into the primary excretory duct, which now becomes the wolffian duct.

Recent investigations have settled the long dispute about the manner of kidney development in favor of a dualistic origin, according to which one anlage gives rise to the secretory, and another to the excretory part. The mesonephros, therefore, like the metanephros, later is formed by a union of parenchyma; that is, glomeruli and secretory tubules, derived from the nephrogenic cord with an outgrowth from the wolffian duct; that is, the collecting tubules. In the metanephros the parenchyma is joined to the pelvis of the kidney by the collecting tubules, both of the latter representing an outgrowth of the original ureter and termed the ureteric tree.

In appearance, structure and organization the mesonephros, therefore, bears such a striking resemblance to the permanent kidney that it may justly be regarded as an abbreviated metanephros.

Depending on its mesodermal derivation, the mature mesonephros is situated anteriorly to the position occupied later by the metanephros; that is, the lower dorsal and upper lumbar or hepatic regions. In relation to the embryo it is large and presents in shape a broad, slightly curved mound or ridge. Its malpighian corpuscles are similar to those of the permanent kidney and show well-developed glomeruli filled with blood and occupying the whole of the capsule. The latter is plainly lined by rather high epithelium. Marked differences exist between the convoluted and collecting tubules. The convoluted tubules bear, except for number, a striking resemblance to those of the metanephros, more particularly in regard to their lining epithelium, which present the general characters of all renal secretory epithelium in convoluted tubules. Mihálkovics[6] describes these cells as high, cylindrical (from 0.01 to 0.02 mm.), of yellowish, poorly staining protoplasm and distinctly granular. But Winiwarter and Sainmont[7] speak of them as cuboid epithelium, which I think is more correct for the intact undegenerated cells. Individually, the cells are sometimes poorly outlined so that, according to Mihálkovics, this epithelium appears in sections frequently like a nucleated yellowish syncytium. The nuclei are relatively large, round and rich in chromatin, and possess, according to Winiwarter and Sainmont, a large nucleolus. In early stages they show frequent mitoses. Mihálkovics describes irregular, colorless, thread-like processes (cilia) extending from the free cell ends into the lumen of the tubules, in which they seem to be continuous with a network which fills the wide lumen. He interprets these pictures as evidences of glandular secretion. Winiwarter and Sainmont also observed the discharge of hyaline globules from these cells which they regard as secretion. I have been unable in the material at my command to discover similar structures except in degenerative processes. As, however, fixation and freshness as well as hardening and staining methods materially influence such details, I do not feel able to deny their existence. Whether or not they really represent products of a secretory activity is, of course, open to question.

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[6] Mihálkovics, G. Von: Untersuchungen über die Entwicklung des Harn und Geschlechtsapparats der Amnioten, Internat. Monatsschr. f. Anat. u. Histol., 1885, ii, p. 41 and p. 65.

[7] Winiwarter, H. Von, and Sainmont, E.: Nouvelles recherches sur l'ovogénèse et l'organogénèse de l'ovaire des mammifères (chat), Arch. de biol., 1909, xxiv, 373. Involution du corps de Wolff.

In the straight and narrow collecting tubules which can be distinguished as easily from the convoluted ones as in the metanephros, the lining epithelium is low (from 0.007 to 0.008 mm., Mihálkovics), closely set, very distinct, clear, with smaller nuclei and resembles the lining cells of the wolffian duct, indicating a close relation of that tubular portion to the excretory duct.

The whole mesonephros is enveloped by a capsule composed in the earlier stages of development by several loosely arranged and cellular layers; in the mature organ, however, the capsule shrinks, and its cellular contents are lost. The parenchymatous or cortical part shows early many undifferentiated blastemic cells lying in a loose, thin stroma. As the tubules develop, these diminish, and in the fully developed mature mesonephros practically no interstitial cellular tissue is to be seen between the tubules of the cortex; but these lie in close proximity, separated only by thin but distinct basement membranes and intertubular capillaries. A thin, loose stroma is retained around the malpighian corpuscles. This is more abundant toward junction with the wolffian duct.

If, then, as will be apparent from the foregoing description, there exists an essential similarity in the organization of the mesonephros and metanephros, there are also, regardless of details, two very important differences, first in circulation, secondly in the connection with the sexual gland. These must, therefore, be shortly described.

The mesonephros enjoys a very rich and peculiar arrangement of its blood-supply. It receives in the first place a large number of arteries from the lateral aortic side. According to Bonnet,[2] there are no less than twenty in the fully-developed human mesonephros, but of even greater abundance is its venous portal circulation (Felix). In order to understand this properly one must recall that the mesonephros lies between the vena cardinalis posterior on the dorsal side and the vena subcardinalis on the ventral side. Both veins are connected at its caudal border with the venae caudalis and ischiadica. Early in mesonephric development numerous branches begin to form between the posterior cardinal and subcardinal veins, traversing the mesonephros. From the beginning the vena cardinalis posterior opens into the duct of Cuvier and through this into the sinus venosus of the heart, while the vena subcardinalis acquires connection with the heart through the hepatic vein (Felix). We shall have reason to refer later to these peculiar circulatory conditions.

The second peculiarity of the mesonephros — its intimate connection with the sexual gland — will be referred to here but briefly, for it will form the subject of a later discussion. At a variable, but very early stage of mesonephric development, a narrow strip of mesothelium extending along the medial surface becomes prominent and cellular, forming the genital tubercle. These cells are later arranged into layers and become definitely differentiated and grouped. The whole mesothelial band is known as germinal epithelium and gives rise to the sexual glands, testis or ovary. A connecting band remains and is known, respectively, as mesorchium or mesovarium.

Lastly, the time over which mesonephric development extends is not uniform in amniotes, even in the mammals, in which it remains a purely embryonic organ. Traces of an early original segmental arrangement have been observed up to human embryos, but the segment stalks fuse rapidly to the nephrogenic cord, so that the early differentiation of the mesoderm is, in mammals at least, much abbreviated.

The time of appearance of the first mesonephric tubules varies. It has been tabulated by Felix, as follows: In the rabbit from the ninth to the tenth day (Köllicker, 1879) 245 hours after fertilization in embryos of from 5 to 5.5 mm. greatest length; a dog, eighteen days, four hours after coition showed from sixteen to twenty primary segment pairs and from eight to seventeen anlagen (Bonnet, 1887). In the pig the first mesonephric anlage is found fourteen days, nine hours after coition in embryos of from 5 to 5.3 mm. greatest length in ten or eleven primary segment pairs; in man the first tubules appear in embryos between 2.6 to 3 mm. greatest length (His, 1880; Keibel, 1896). The mesonephros is reported as complete in the guinea-pig on the twenty-third day after the last litter (Weber, 1897); in rabbits between 18 and 20 mm. length (Mihálkovics), or on the sixteenth day of development (Egl, 1876); in sheep of from 18 to 20 mm. length (Weber, 1897); in pigs of from 6 to 7 cm. length (Keibel, 1897; Neuhauser, 1903); in human embryos of 7 mm. length (Weber, 1897; MacCallum, 1902), and in the mouse the development, as mentioned, remains incomplete and no glomeruli are formed (Weber, 1897). When the mesonephros has reached its caudal limit, no new caudal anlages are added in older embryos, and a degenerative and destructive process becomes generally manifest which annihilates the organ with the exception of those anterior and middle parts which enter the services of the sexual organs. The manner, character and bearing of this process will form the subject of the following special part.

II. SPECIAL PART

The degeneration and ultimate fate of the mesonephros have been much discussed by anatomists from the developmental point of view, but the histological changes leading to its loss, their causes and possible bearing on certain problems of postnatal pathology have hardly received any attention. Nearly thirty years ago (1885) Mihálkovics[6] contributed in a classic work an investigation and description of the histological details. Nothing has been added since, with the exception of the recent work on the organogenesis of the cat's ovary (1909) by Winiwarter and Sainmont,[7] who describe the degenerative appearances in the mesonephric tubules with care; and in the two most complete expositions of the subject by Felix, the one in Hertwig's "Handbuch der Entwicklungsgeschichte," the other in Keibel and Mall's "Human Embryology," only a short summary of Mihálkovics' observations are given. But this matter is perhaps of greater pathological than embryological interest, for these phenomena resemble very closely the changes in certain metanephric diseases. Nevertheless, they occur without bacterial or outside toxic invasion, but as a part of a *normal* developmental process. They deserve, therefore, special recognition and study by the pathologist.

The degeneration of the mesonephros commences early in mammals. In the human embryo, according to Felix, even before the mesonephric development has been caudally completed, in an embryo of 5.3 mm., it involves primarily the most cranial tubules and proceeds rapidly to embryos of 21 mm. This constitutes the first and essential part of mesonephric degeneration. The second period is said by Felix to commence very gradually, progresses slowly and is characterized by incorporation of the middle mesonephric portion into the genital system. All other parts undergo complete retrogression. It will be remembered that of the remaining parts in the female (paroophoron, duct of Gärtner, parovarium), none retains any visible function, while in the male (vasa efferentia, coni vasculosi, paradidymis, epididymis, vas deferens, ejaculatory duct, seminal vesicles), the mesonephric remnants become new functionating structures.

A study of the degeneration of the mesonephros involves necessarily the consideration of three questions:

1. What are the histological changes leading to annihilation of the organ?
2. What is their cause?
3. What is their significance?

1. It has already been noted that the most complete study of the histological changes leading to loss of the mesonephros is that of Mihálkovics made in 1885. This description is so excellent and characteristic that I shall quote it in full. Mihálkovics studied the lesion in chicks,

commencing with the eighth to ninth day of incubation, and in rabbits of from 16 to 18 mm. lengths: at these times the formation of mesonephric buds and tubules has practically come to a standstill, the tubules no longer develop convolutions, but remain stationary, while the large venous sinuses recede and assume the dimensions of usual blood-vessels. The interstices and recesses thus formed are filled by connective tissue which previously has existed only sparingly and loosely between the tubules. At the same time the epithelium of the convoluted tubules gradually loses the character of secretory cells and assumes the shape of ordinary cylindrical cells with a greater affinity for stains than possessed before. The tubules persist in this state, in chicks, from the eighth to the sixteenth or seventeenth day, in the rabbit to a length of from 3.5 to 4 cm. Then they commence to obliterate. The first evidence of this obliteration is a narrowing of the convoluted tubules with a progressing small-drop fatty degeneration of the lining cells. Ultimately the cell bodies undergo a fatty dissolution and fill the lumen of the tubules. Instead of canals there remain thus solid cell cords which consist of still recognizable tubular cells. These are more or less concealed by the richly cellular stroma and may, therefore, escape attention. In the meantime the malpighian corpuscles have become involved in the process. Their loss commences with obliteration of the afferent vessels, and the atrophic glomerulus no longer fills the capsule, but leaves a space between the tuft and capsule wall. Finally, the capsule, following the receding glomerulus, retracts and becomes attached to the tuft. In sections these remnants of malpighian corpuscles resemble cell buds or groups lying between obliterating mesonephric tubules. One other point was fully noticed by Mihálkovics, although he drew from it no theoretical or hypothetical conclusions, namely, that as the mesonephros shrinks, the medially attached genital gland enlarges, thus reversing the relative size of the two organs: "Primarily the small genital gland rested on the medial side of the massive mesonephros; after its contraction insignificant rests of the mesonephros lie on the lateral side of the now huge genital gland." Mihálkovics, however, did not trace further the details of this impressive phenomenon. Later investigations have generally recognized and recorded it also without further comment.

The recent observations of Winiwarter and Sainmont on the organogenesis of the cat's ovary have supplemented in certain details Mihálkovics' work. They found that the transformation of those mesonephric parts which go to form epoophoron and paroophoron commences with a pigmentary degeneration of the lining cells of the convoluted tubules. This epithelium becomes swollen, coarsely granular and later desquamated, and in advanced degeneration narrow tubular canals are found whose lumen is filled by pigment-granules. It will be observed that the changes described by Mihálkovics and Winiwarter and Sainmont bear close resemblance to pathological lesions. A further study, especially regarding their histogenesis and causes, seemed, therefore, desirable, for such knowledge might prove of value in the interpretation of pathological processes.

The material at my disposal was by force of circumstances limited, so that observations could not be made on a desirable extensive and detailed scale. Much remains hidden which must be cleared by future investigation. But the results are perhaps of sufficient interest to warrant this fragmentary report, more especially as they differ somewhat from previous views.[8] The available material consisted of rabbit embryos from the fourteenth to the twenty-sixth day of intra-uterine life, and marsupial embryos of *Dasyurus viverrenus,* beginning with the fifth to sixth day and extending to the nineteenth day. To obtain the full age of these embryos, about eight days intra-uterine life must be added.

These periods comprise from the early to the most active stages of mesonephric destruction. The lesions appeared essentially the same in both animals. The results are, therefore, presented together.

Certain histological modifications distinguish the destruction of the anterior portion of the mesonephros, which enters the service of the sexual gland from the posterior one, which is completely lost. The involvement of both, however, becomes evident immediately after beginning growth of the sex gland and goes hand in hand with the latter's development and differentiation. In rabbits this commences from the fourteenth or the fifteenth day, in the dasyurus after about nine days of marsupial life, and then proceeds with great rapidity. To begin with the changes in the anterior portion of the mesonephros which lies in closest contact with the sex gland: when an enlargement of the sex gland, which until then has only formed a thickening or tubercle on the medial mesonephric side, is noticeable, there occurs in the vicinity of attachment to the mesorchium or mesovarium a small cell proliferation which leads by rapid extension to a marked interstitial cell infiltration of the neighboring parts. It thus involves diffusely the periglomerular tissue, but also spreads peripherally under the outer capsule. From these points it penetrates by streaks into the glandular parts between the convoluted tubules.

The periglomerular infiltration surrounds and compresses the malpighian corpuscles, and involving Bowman's capsule, invades their interior and gradually obliterates it. The replacing cells have all the appearances of connective-tissue cells; first round, they soon acquire a distinct small and large spindle shape. During this process the glomerular tuft is much engorged, and hemorrhagic extravasations into the capsule, sometimes sufficient to destroy the whole tuft, may occur. This loss of malpighian corpuscles in the anterior portion appears to be one of the earliest and most rapid manifestations of mesonephric degeneration.

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[8] I intend to publish at some later day a full, illustrated account of mesonephric degeneration.

Proceeding from this focus, streaks of interstitial cells extend to the territory of the tubules, where they meet similar invading cells from the subcapsular tissue. This progress leads to marked thickening of the previously very thin intertubular septa of the convoluted tubules, and is associated with a rather irregular engorgement and dilatation of capillaries.

Coincident and probably not, or at least not solely, dependent on this cell infiltration, is marked parenchymatous degeneration of the cells lining the tubules, closely followed by desquamation and proliferation of this epithelium. The cells become succulent, swollen, coarsely granular, in many pigmentary granules appear, or small to large vacuoles (fat?) and hyaline drops. They are then desquamated as a whole, or discharge granular masses and pigmented granules into the lumen, forming casts. The nucleus is well preserved to the last, and seems to succumb by karyolysis.

Proliferation of the epithelium is very active, so that frequently several cell layers are formed. But the new cells are soon overtaken by a similar fate. In tubules in which the cells appear more resistant or are perhaps later attacked, they seem to become higher and narrower, cylindrical, as Mihálkovics terms it, before they also undergo disintegration.

Ultimately, the tubules are invaded and compressed by interstitial cells from the septa, broken and obliterated. The collecting, straight tubules remain well preserved until late and are apparently lost by cell overgrowth without exhibiting the degenerative changes so conspicuous in the convoluted tubules.

Thus the anterior part of the mesonephros is generally overgrown by cellular fibrous tissue and contracts, and the remaining uninvolved tubules of the middle portion are drawn toward the territory of the meanwhile enormously enlarged sex gland, where they may be recognized for some time surrounded by richly cellular connective tissue.

Somewhat different seems to be the fate of the posterior portion of the mesonephros which is doomed to complete annihilation. Degenerative features seem to predominate in it almost entirely, and sclerotic changes do not take an active part in its destruction.

The changes appear very nearly about the same time as anteriorly, possibly somewhat later. Toward the end they proceed with great speed.

The glomerular coils become cellular and show swelling, turbidity and gradual fusion of capillary loops. This may involve at a time only a number of loops, and the remaining ones show then a marked capillary dilatation and engorgement. The fused coils become generally adherent to some part of the capsule, very much as in nephritis, the glomerulus retracts and the capsular space is widened. The capsule wall shows usually swelling, but no cellular thickening, and remains intact until the whole capsule collapses from loss of the glomerulus. Such pictures resemble those described by Mihálkovics, but I have been unable to observe the swelling and obliteration of the glomerular afferent vessel to which he ascribes glomerular retraction and loss. On the other hand, the degenerative changes in the convoluted tubules are similar to those in the anterior portion, and there exists also irregular intertubular engorgement and dilatation of capillaries.

Cell overgrowth, which forms so conspicuous a feature of the destruction of the anterior part, is posteriorly absent in the beginning. Only later, in advanced degeneration, foci of spindle-cells are seen between the tubules, around capillaries, and somewhat more abundantly at the periphery under the capsule. It is not possible to state how far they may enter into the very last phases of destruction. These are very difficult to determine, as they proceed with extraordinary rapidity. In rabbits the whole disappearance is carried on from the nineteenth to the twenty-sixth day, and the final solution of the posterior part between the twenty-first to the twenty-fifth day. On the twenty-fifth day very little remains.

During the early stages of the lesion, new tubules are said to be formed. Felix attributes these either to scattered cells in the surrounding mesoderm or to budding of tubules and malpighian corpuscles. With regard to this it may be stated that no evidences of budding of either tubules or malpighian corpuscles were seen in this series, although cell proliferation within tubules and glomeruli occurs.

The lesions briefly described above attract attention on account of their similarity in character, genesis and distribution to certain types of degenerative and productive nephritis. Indeed, so close is this relation that one may speak of an acute destructive mesonephritis.

An investigation into its cause and significance seems, therefore, worth while.

2. Three possibilities may be entertained in regard to the cause of mesonephric retrogression:

A. It may be due to crowding of the tubules within a small space. To this has been attributed the early involvement of the most cranially situated tubules. Felix, however, regards this as a very subordinate, if any, cause for the reason that the mesonephric arteries show at no time any indication of crowding by being bent in their course, but, on the contrary, remain perfectly horizontal. There is, moreover, as seems to me, no histological evidence of crowding at any time, nor is the histogenetic picture of the retrogression itself in harmony with this view.

B. Mesonephric loss may be essentially due to interference and obliteration of its blood-supply. This is also not borne out by the facts.

In the first place, the degeneration commences at a time when the mesonephric blood-supply is still quite adequate and sufficiently intact to allow the formation of new tubules. In the second and most important place, the histological picture corresponds in no way to what is to be expected after quantitative interference with the blood-supply of an organ. Two things may occur as the result of this, atrophy or infarction. Here we have neither, but an extensive active cellular proliferation and invasion associated with a characteristically located rapid parenchymatous degeneration. Both go far beyond the limits of the results of simple quantitative interference with the vascular supply of an organ. Furthermore, the irregular streaky advance of the lesion, attacking certain parts while others are still intact, the capillary engorgement, degenerative cell waste and parenchymatous and interstitial cell proliferation leading to extensive cicatrization relate it to the inflammatory conditions.

C. There remains then the possibility of an influence which is conveyed to the mesonephros from other parts. In this connection attention is immediately arrested by the peculiar relation in which growth and development of the medially attached sex gland stand to mesonephric destruction.

They commence in closest association with each other and progress in inverse ratio. Indeed, rapidity of growth and differentiation in one, and corresponding destruction and loss of the other are impressively associated. In particular, the earliest and most pronounced changes leading to loss of malphigian corpuscles in the anterior part take place at the point of most intimate connection, and the degeneration appears to acquire momentum with progressing maturity of the genital gland. We are confronted, therefore, by the question of a possible antagonistic influence of the latter on the mesonephros, and it is necessary to inquire how well such an idea is founded.

3. The idea of antagonism between cells, tissues and organs is by no means new. It has been emphasized by several biologists that among the forces which shape phylogenetic and ontogenetic evolution, antagonism between organs may be of as great an importance as correlation or altruism. As early as 1876 Boll, in "Princip des Wachsthums," said:

> Microscopic investigation has demonstrated in the peaceful egg the existence of highly dramatic processes which, out of compliment to a much-beloved terminology of doubtful value, I shall link together under the title of "the struggle of the tissues."[9]

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[9] Die mikroskopische Untersüchung hat im Frieden des Eies die Existenz höchst dramatischer Vorgänge nachgewiesen, welche ich aus Konzession an eine sehr beliebte Terminologie von zweifelhaften Werthe unter der Bezeichnung des *Kampfes der Gewebe* züsammenfassen will.

It is well known that Roux has elaborated these ideas in his well-known monograph, "Der Kampf der Theile im Organismus," and recently von Hansemann, in "Deszendenz und Pathologie," has added another illuminating discussion of the subject. The individual organism reflects to a great extent the forces which move a community of individuals. In phylogeny, correlation and altruism of individuals are supplemented by a necessary antagonism to insure preservation and progress of the individual within the community; in ontogeny similar forces are repeated in the relation of cell to cell, tissue to tissue, organ to organ. Thus weak and unnecessary organs which can no longer hold their own in the community of organs are removed, and the organism is freed from what would otherwise be a disadvantageous burden in its evolution. We have certain reasons to suspect that on such antagonistic actions rest the disappearance of various embryonic structures, the thymus, for example; but in most instances this suspicion can only be vague. The case under discussion, however, presents apparently a definite instance of growth and development of one organ at the expense of another. How is this accomplished?

Goethe, St. Hilaire and Roux have drawn attention to the fact that nutritive struggle plays an important rôle in mutual antagonism, for if one part receives for its growth a large supply of the available nutriment, others must suffer. They termed this the law of compensatory growth. Darwin, however, while admitting its importance, rather regarded it as a subordinate influence. Roux believes, nevertheless, that such nutritional influences are by no means always of the ordinary direct mechanical circulatory nature, but of a much more complicated character. He draws attention to the fact that women who nurse for years are very susceptible to osteomalacia because, he believes, of constant withdrawal of calcium salts in the milk, which is, therefore, unavailable for the bone. The antagonism or, as he calls it, "struggle of the mammary glands with the bones," is characterized by greater strength of the former to attract and hold calcium salts. Later investigators have endeavored to trace this to a direct influence of the sex gland. It is possible that a nutritive struggle may enter into the antagonistic relations of mesonephros and sex gland. But it must be considered doubtful whether it can be regarded as the sole cause of mesonephric loss, for certain features distinguish this from nutritive disturbances. The mesonephros is apparently attacked by a distinctly irritative, destructive and, if the term is permissible, formative stimulus which leads to its speedy exitus.

Again, in modern investigations many phenomena of organic interrelation are attributed to hormones. Hormones may be defined as messengers from one organ to another which either excite or inhibit functional activities. The process under consideration can, therefore, hardly be grouped within the ordinary understanding of hormone action.

Its exact nature remains unknown.

Even if we were obliged to leave this point in abeyance, however, we may go further and ask whether the possibility of similar antagonism between organs may not outlast embryonic life and continue throughout postnatal existence. Here we touch on points of great importance to the pathologist. We are dealing in the embryo, as has been shown, with a mesonephritis which cannot be attributed to bacterial or an outside toxic influence. It is the result of a true auto-intoxication. We may, therefore, ask more specifically, whether similar phenomena continue after birth. In other words, if, as seems highly probable, antagonism of organic units is one of the moving forces in the life of all individuals from practically the first division of the ovum to death, may it not enter more than hitherto supposed into production, manifestation and outcome of diseases? Perhaps etiology has for practical reasons been too anxious to attach an almost exclusive importance to external causes of disease, and has neglected a study of those internal conditions which prepare and make possible the development and specificity of morbid processes.

The consideration of these problems reaches at present the borderland of pure speculation; but future investigations may put them, like many other at first sight phantastic views, on a sound disputable basis.

Finally, we must record what is known of any possible function of the mesonephros in animals in which the renal activity has been handed over to the metanephros.

Has the persistence of the mesonephros through at least part of the evolution of the individual any significance? This problem is intimately connected with the previous one.

Johannes Müller, who discovered its capillary tufts, believed that the wolffian tubules secreted urine which passed through the wolffian duct into the cloaca or allantois.

Mihálkovics came to the conclusion that the amniotic metanephros does not, in all probability, assume the functions of urine secretion suddenly or abruptly, as a considerable part of the wolffian body still exists at a time of advanced development of the metanephros. There exists, in his opinion, a period when both organs functionate jointly as excretory organs. Mihálkovics sought support of this contention in the phylogenetic history of the mesonephros, particularly in its continuation through the early part of postnatal life in reptiles. This, in Mihálkovics' opinion, would indicate that among the lowest forms of amniotes the metanephros is assisted in some way and at least for a time by the mesonephros. He concludes that in the evolution of amniotes there existed antecedents, now extinct, in which the mesonephros persisted throughout life, while the metanephros remained incomplete and small. This first anlage of the metanephros gradually developed through increasing and complicated demands to the size and importance of the present organ.

Bonnet[2] also states that he has found urine in the mesonephric tubules of pig embryos commencing with 1 cm. length and in the metanephric tubules in embryos from 8 cm. length.

In man the mesonephros acquires, as already emphasized, a considerable high state of differentiation. There are, nevertheless, certain points which speak against its excretory activity in man. Most important is in this respect its early degeneration, which, according to Felix,[2] commences even before the organ has fully developed. Again, man lacks a vesicular allantois and urinary bladder in early life, and the urogenital sinus does not open to the outside until the embryo has reached a length of 14 mm. (Bonnet). Bonnet states that the excretion of nitrogenous waste-products and elimination of water probably take place in the region of the allantois or by the chorionic circulation, and later by the umbilical vessels in the placenta. It is, therefore, generally held that the mesonephros in mammals and particularly man possesses no excretory renal function.

Is then the mesonephros a purely rudimentary organ which enters in no way into the welfare of the organism? Its very existence and high grade of differentiation would argue against it, for complete loss of function leads usually to either entire loss or a very incomplete appearance of an organ in later stages of phylogenetic evolution. This, for example, is the case with the pronephros, whose very incomplete appearance in higher amniotes excludes almost with certainty the possibility of any function whatever.

Following and guided by the history of some other organs of internal secretion, an effort has lately been made to find similar evidences for the mesonephros; but practically very little has been accomplished in this regard.

The recent observations of Kermauner[10] offer perhaps a clue in this direction. According to him the absence of the wolffian bodies is incompatible with life and leads to early death of the fetus. He, therefore, regards the mesonephros of higher animals no longer as an organ of excretion, but of internal secretion (hormones) and assimilation. Kermauner points in support of this idea to the rich blood-supply of the

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[10] Kermauner: Das Fehlen beider Keimdrüsen, Beitr. z. path. Anat., von Ziegler (now Marchand and Aschoff), 1912, liv, No. 3, p. 478.

Wolff, B.: Ueber foetale Hormone, in Handbuch der Biochemie von Carl Oppenheim, Ergänzungsband, 1913.

mesonephros with the numerous segmental arteries and veins which go to form its characteristic portal circulation.

He concludes that the wolffian body is essential for certain periods of life, first in the development of the placenta, and secondly in complementing assimilative functions of other fetal parts until the appearance of permanent organs, notably the liver, renders this unnecessary. The specific functions of the wolffian body are then no longer required, the fetus passes to new phases of life, and the mesonephros makes its exit.

It must, however, be mentioned in this connection that the anlage of the mesonephric portal circulation in man is, according to Felix, only very short-lived, since in his observations the subcardinal veins and the transverse mesonephric branches are in act of degeneration in an embryo of 12.5 mm. greatest length. Kermauner's views are in their attempt of direct definition of mesonephric functions at the best very hypothetical, and need additional facts for sound basis. On the other hand, it is of course well known that certain organs of internal secretion or specific metabolic activity[11] functionated originally as organs of external secretion. They present, therefore, the peculiar phenomenon of functional mutation during phylogenetic evolution with morphological persistence. Perhaps the thyroid gland furnishes the best example of this type, for whether we agree with Gaskell's extreme view that these glands were originally uterine, or whether we regard them, more conservatively, as derivatives of mucous glands,[12] the fact remains that they have undergone a functional mutation but have retained the acinar tubular structure which is characteristic of glands with an external duct.

Two possibilities may exist in this transformation of glands of external secretion to glands of internal secretion and specific metabolic functions. First, the glands possessed originally only the function of external secretion, and the others have been acquired or developed entirely *de novo* after the usefulness of the gland as an organ of external secretion has been ended.

This would seem an unsatisfactory and unintelligible explanation, for it accounts in no way for the manner in which the new functions originated while structure and arrangement of the parts continued. On the contrary, one would expect here as in other tissues that loss of function would go hand in hand with loss of structure or alteration in function with alterations in structure and rearrangement of parts. This is the rule under physiological and pathological conditions.

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[11] I use the two terms "internal secretion" and "specific metabolic activity" because the influence of these glands may be due to other factors besides internal secretion. Certain observations by Milne and Peters (Observations of the Glycolytic Power of the Blood and Tissues in Normal and Diabetic Conditions, Jour. Med. Research, 1912, xxvi, 415) make this probable for the pancreas.

[12] Gaskell: See Footnote 2. For the evolution of the ductless glands consult Hertwig's Handbuch der Entwicklungsgeschichte.

A second possibility seems, therefore, much more plausible and stands on some facts: glandular organs possess from their origin functions of external and internal secretion and specific metabolic activities. The exercise of these is initiated, developed and modified by the environment. If thus, through evolutionary agencies, the necessity or even possibility for external secretion no longer exists, it ceases, but the gland still retains its functions of internal secretion and specific metabolism. If now, further, no soil for this internal secretion has been developed,[13] or if the activity as a special metabolizer is no longer required, the gland is lost from disuse. It is very possible that under such circumstances its removal is expedited by the antagonistic action of other glands. If, however, a receptive soil for its internal secretion has been created and is retained during consecutive periods, or if its specific metabolizing function is adapted for succeeding evolutionary stages, the gland is not only retained, but strongly specializes under these stimuli in either one or both of these directions. It may thus acquire an even greater influence on the internal economy of the organism than it formerly possessed with divided functions and, in turn, may play an important part in future evolution.

We know, for example, that man still possesses several glands with external secretion which in addition are capable of and do exert strong internal influences, notably the testicle and the pancreas. The older idea that these organs contained specific structures for internal secretion or special metabolic purposes has been replaced by the probably more correct view that the whole of the gland's parenchyma is potent in these regards. This is certainly true of the pancreas,[14] probably also of the testicle, for while an internal secretion has been attributed to its interstitial cells, it seems certain that the glandular secretion which, moreover, is discharged only at relatively long intervals, exerts a very decided influence particularly on muscles and brain.

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[13] In discussions of the disorders of internal secretion, perhaps insufficient attention has been paid to the importance which the soil may exercise in this connection. It is evident, however, that the effect of an internal secretion depends not only on the function of the gland, but also on the condition of the particular soil which has become receptive to the secretion. It would seem, therefore, that disturbances may arise not only through glandular disorders, but also through developmental or acquired faults of the soil. This mutual relation may play an even greater part when close anatomical and physiological connections existed during embryonic life. Finally, it seems not improbable that internal secretions may be modified on their way by passage through other glands. This opens another opportunity for variations.

[14] Milne and Peters: See Footnote 10. Potter and Milne: Bronzed Diabetes, Am. Jour. Med. Sc., 1911, cxliii, 46.

The interesting and peculiar mutation of function with morphological persistence in glands is then rendered intelligible when we regard it as a relative one, representing rather a specialization than a new acquisition. The rôle which these organs are to play in life and the duration of their existence are determined by first, the period of evolution at which the mutation occurs, secondly, the nature of their internal secretion or metabolism, and thirdly, their relationship to a particular soil or phase of general metabolism. Consequently these organs become arranged according to periods of evolution, and appear and disappear with them. Here as elsewhere ontogeny appears as a recapitulation of phylogeny.

The mesonephros, although short-lived, may, nevertheless, exercise an influence on human fetal life and development not unlike that of other fetal and infantile structures. It cannot, in view of what has been presented above, be denied. But this question is, like the others, still far from being solved, and we possess to-day only two definite observations in this regard: its complete and high degree of development and differentiation, and the statement advanced by Kermauner that its absence is not compatible with life. A third, but much more uncertain, point might be construed from its relation to the genital gland. This appears to owe its inception, growth and differentiation to the mesonephros, which it ultimately consumes. Finally, a fourth, but equally uncertain conclusion, might be drawn from the histological pictures observed by Mihálkovics and Winiwarter and Sainmont. These may indicate a secretory activity. But we know from observations of the adult metanephros that such pictures are misleading[15] and not conclusive.

These, then, are some of the problems which confront us in the study of renal evolution.[16] That their bearing is not only of special, but also of very general pathological interest, seems not doubtful. I enter these pages as a plea for their investigation and for a more careful consideration of ontogeny and phylogeny by pathologists.

I have in conclusion many grateful acknowledgements to make: Prof. Arthur Keith, F. R. S., director of the Hunterian Museum at the Royal College of Surgeons, London, allowed me study of his specimens and put his technical assistant at my disposal. Prof. James P. Hill, F. R. S., of University College, London, gave me free use of his collection of *Dasyurus viverrenus* and much advice. To Prof. Richard Assheton, F. R. S., of the University of Cambridge I am particularly indebted, not only for many carefully selected sections of rabbit embryos, but also for a great deal of active help and counsel. Last, not least, to my colleagues in the Gordon laboratory, Guy's Hospital, Drs. Laidlaw, Goodhart and Chisholm, I owe material and constant kind and helpful interest.

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[15] Aschoff, L.: Zur Morphologie der Nierensekretion, Verhandl. d. deutsch. path. Gesellsch., Jena, G. Fischer, 1912.

[16] I have not touched at all in this communication on any possible differences in this process between male and female and, further, what determines the preservation and subsequent incorporation into the sexual system of certain mesonephric tubules. These problems need special investigation.

A METHOD DEVELOPED FOR OBTAINING A STANDARD WASSERMAN ANTIGEN *

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This method has been developed in the Pathological Department of Bellevue Hospital during the past six months as a result of a study on the routine Wassermann reactions of five thousand patients. These patients have stayed in the hospital three days or longer; otherwise there has been no choice of subjects.

For a long time it has been felt that the only variable reagent in the Wassermann reaction has been the antigen. Antigens have been made up from the alcoholic extracts of human syphilitic livers, human hearts and ox-hearts. The values of these various antigens have differed considerably in each batch made up. This is apparently due to variations in the organs from single individuals. For this reason the extract from guinea-pig hearts has been preferred because a larger number can be used for each batch of antigen, so that the individual factor is reduced to the vanishing-point.

TABLE 1.—Readings with the Same

Antigen	Serum A Antigen, Dil., c.c.							Serum B Antigens, c.c.							Serum C Antigens, c.c.						
	Control	1.	0.8	0.6	0.4	0.2	0.09	Control	1.	0.8	0.6	0.4	0.2	0.09	Control	1.	0.8	0.6	0.4	0.2	0.09
Antigen 1	0	3	3	3	3	2	0	0	3	3	3	3	3	2	0	3	3	3	3	0	0
Antigen 2	0	3	3	3	3	3	0	0	3	3	3	3	3	1	0	3	3	3	3	1	0
Antigen 3	0	3	3	3	3	1	0	0	3	3	3	3	3	3	0	3	3	3	3	0	0
Antigen 4	0	3	3	3	3	2	0	0	3	3	3	3	3	2	0	3	3	3	3	3	0
Antigen 5	0	3	3	3	3	3	0	0	3	3	3	3	3	2	0	3	3	3	3	1	0
	High, 15; low, 13.							High, 18; low, 16.							High, 15; low, 12.						

* In Tables 1 and 2, 0 = complete hemolysis, 1 = marked hemolysis, 2 = slight hemolysis Twenty-three other cases were 0. All these cases were specific as to history or lesion. Forty other serums were negative.

THE METHOD IN DETAIL

The method of conducting the Wassermann reaction in this laboratory is as follows:

Patient's Serum.—The patient's serum is poured off from the clotted blood and centrifuged. The clear supernatant serum is removed and

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inactivated at 56 C. for half an hour. A test-tube rack containing seven test-tubes is set up, and for the half quantity of the original Wassermann reaction 0.1 c.c. of the patient's serum is pipetted into each tube.

Complement.—The complement is obtained by bleeding at least three guinea-pigs and removing the serum after from twelve to eighteen hours. This serum is diluted 1 part of serum to 8 of physiological salt solution; 0.5 c.c. of this diluted complement is added to each one of the seven tubes.

Indicator.—The indicator used to detect the presence or absence of the complement is 0.5 c.c. of a 5 per cent. suspension of sheep-cells, to which has been added 0.5 c.c. of a dilution of amboceptor of such strength that each cubic centimeter contains four hemolytic units. This mixture is allowed to incubate at 37 C. for half an hour before being added to the Wassermann system. It has been found from a study of over ten thousand Wassermann reactions that the native amboceptor occurring in human blood may be disregarded if this be done.

SERUMS WITH FIVE DIFFERENT ANTIGENS*

	Serum D Antigens, c.c.							Serum E Antigens, c.c.							Serum F Antigens, c.c.							Serum G Antigens, c.c.					
Control	1.	0.8	0.6	0.4	0.2	0.09	Control	1.	0.8	0.6	0.4	0.2	0.09	Control	1.	0.8	0.6	0.4	0.2	0.09	Control	1.	0.8	0.6	0.4	0.2	0.09
0	3	3	3	3	0	0	0	3	2	1	0	0	0	0	3	3	3	3	3	0	0	3	0	0	0	0	0
0	3	3	3	2	0	0	0	3	3	3	0	0	0	0	3	3	3	3	3	0	0	2	0	0	0	0	0
0	3	3	3	3	0	0	0	3	3	2	0	0	0	0	3	3	3	3	2	0	0	3	1	0	0	0	0
0	3	3	3	2	0	0	0	3	3	1	0	0	0	0	3	3	3	3	3	0	0	3	0	0	0	0	0
0	3	3	3	1	0	0	0	3	3	3	0	0	0	0	3	3	3	3	1	0	0	2	1	0	0	0	0
	High, 12; low, 11.							High, 9; low, 7.							High, 15; low, 13.							High, 4; low, 2.					

and 3 = no hemolysis.

Antigen.—The antigen that is now used is an alcoholic extract of guinea-pig hearts to which has been added enough cholesterin to bring it to the half-saturation point. When the pigs are killed the heart is removed, and all blood present in the cavities is removed by massaging with a clean towel. The heart is weighed, this weight being recorded on the jar in which the heart is preserved until a sufficient amount has accumulated. In preparing this antigen at least 300 gm. of guinea-pig heart, after having been finely ground, is extracted for fourteen days at 37 C. with 3,000 c.c. of absolute alcohol, chemically pure. It is then filtered, and half the filtrate is placed in a flask and an excess amount of chemically pure cholesterin is added. It is allowed to stand in the incubator over night. The next morning the flask is removed from the incubator and placed in a constant temperature bath at 16 C. for three hours. This is to precipitate the excessive amount of cholesterin. It is now filtered and this saturated cholesterin solution is added to an equal quantity of the filtered alcoholic extract. Twenty cubic centimeters are removed with a pipet and placed in a weighed dish and evaporated at 56 C. to dryness. It is then placed in a desiccator for twenty-four hours over sulphuric acid and then weighed. It is thus determined what the total lipoid cholesterin concentration of this alcoholic solution is. After having determined this, it is tested for its anticomplementary effect.

In all, five different lots have been made up by this method, and they have been remarkably constant in their total lipoid concentration and their anticomplementary value, and, as will be seen from Table 1, in their antigenic value.

Dilution for Use.—One cubic centimeter of the alcoholic extract is added to as many cubic centimeters of salt solution as is necessary to make the lipoids and cholesterin weight equal to 0.1 mg. per cubic centimeter. That is, if 100 c.c. of the alcoholic extract contain 0.780 gm., we add 1 c.c. of this to 77 c.c. of physiological salt solution. This is the first antigen dilution, and 1 c.c. is placed in the second tube in the rack (the first tube containing only salt solution and no antigen, this being the control). In the third tube is placed 0.8 c.c. of this antigen dilution; in the next 0.6; in the next 0.4; in the next 0.2, and in the next 0.09. This gives us a series of antigen tubes with decreasing amounts of antigen and a constant amount of serum. Enough 0.8 per cent. sodium chlorid solution is added to each tube to make the total volume 1.6 c.c. The antigen can be diluted with the sodium chlorid solution before it is added to the tube; this is perhaps easier to do. The reading is made as soon as a control set of tubes containing complement and the various strengths of antigen, and the control tube in the individual set, show complete hemolysis.

Only four degrees of hemolysis are observed in the tubes: zero, equaling complete hemolysis; 1, marked hemolysis; 2, slight hemolysis, and 3, no hemolysis. In this way, having three degrees of inhibition for each tube and six antigen tubes, we have a total possibility of eighteen units, provided complete inhibition occurs in all these tubes. Less than 0.5 per cent. of all positive cases give eighteen or more units.

Duplicate tests of patient's serum, unknown as duplicates to the person who made the readings, came out within one or two units of each other constantly. The tests on the five different batches of antigen made up with this procedure have shown no greater differences with the same serum, that is, one or two units. This is a much more constant reading than we have been able to obtain with any antigens heretofore. With this method the antigen is practically as constant in quality as is the amboceptor or complement.

Table 1 shows a series of readings with the same serums with the five different antigens. Table 2 shows duplicate serum readings with one of the antigens.

TABLE 2.—Duplicate Serum Readings with One of the Antigens

Serum	Control	1.	0.8	0.6	0.4	0.2	0.09	Units of Serum	Units in Sp. Fl.
J. K.	0	3	3	3	3	3	0	15	15
	0	3	3	3	3	3	0	15	
T. R.	0	3	3	3	3	2	0	14	
	0	3	3	3	3	3	0	15	
P. C.	0	3	3	3	3	3	2	17	15
	0	3	3	3	3	3	2	17	
J. L.	0	3	3	3	3	3	2	17	
	0	3	3	3	3	3	1	16	
M.	0	3	3	3	0	0	0	9	
	0	3	3	2	0	0	0	8	

CONCLUSIONS

1. The cholesterin, guinea-pig heart antigen is readily obtained and constant in its antigenic value. (This has already been suggested by Swift and Ellis and others.)

2. A series of dilutions of the antigens is obtained by weight, which has been shown to give constant results.

3. A Wassermann reaction may now be standardized so that the readings will agree very closely in far distant laboratories.

4. In the use of this antigen the patient's serum must be inactivated.

5. There must be more than two units of complement.

6. The red cells must be sensitized by the amboceptor before being added to the system.

This antigen has been criticized as being too delicate and as giving positive results in non-specific cases.

More than five thousand cases were run in duplicate, one set with this antigen and the other with an acetone-insoluble antigen from ox-heart. There were 8 per cent. positive with the cholesterin guinea-pig heart which were negative with the ox-heart, but in none of them was it possible to exclude syphilis; in fact, the vast majority of them showed luetic infection or the results of such an infection, or had a positive history.

A more detailed paper will be published later, giving the results of this method as applied to treatment and in the individual variations of the Wassermann reaction in the same individual over various periods.

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A STUDY OF THE ACTION OF ATROPIN ON THE EOSINOPHIL CELLS OF THE BLOOD *

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Our knowledge of the functions of the eosinophil cells is slight. The most important and perhaps the only well-demonstrated function of these cells is their association with the reaction of the body to the invasion of alien protein. The notable rise in number of eosinophils in the circulating blood following the parenteral introduction of various proteins is now well known. By the work of Schlecht,[1] Schlecht and Schwenker,[2] Schittenhelm, Weichardt and Grisshammer,[3] Stäubli,[4] Herrick,[5] and Ahl and Schittenhelm[6] it has been thoroughly established that the subcutaneous, intraperitoneal or intravenous introduction of alien proteins at longer or shorter intervals is followed by a definite eosinophilia of the blood. Particularly is this a feature of the post-anaphylactic stage following the injection of protein at intervals of five days or more. The eosinophilia following administration of diphtheria antitoxin and of tuberculin has been recognized for a still longer time. Possibly the eosinophilia observed during convalescence from various infections is a manifestation of the same response on the part of the living organism to the invasion of foreign protein.

Since the problem of immunity is bound up with that of the adaptation of the body to alien protein material, and since the eosinophils have such close relation to the process, any study throwing light on the

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* From the Department of Practice of Medicine, College of Physicians and Surgeons, Columbia University, New York.

[1] Schlecht: Ueber die Einwirkung von Seruminjectionen auf die Eosinophilen und Mastzellen des menschlichen und tierischen Blut, Deutsch. Arch. f. klin. Med., 1910, xcviii, 308.

[2] Schlecht and Schwenker: Ueber die Beziehungen der Eosinophilie zur Anaphylaxie, Deutsch. Arch. f. klin. Med., 1912, cviii, 405.

[3] Schittenhelm, Weichardt and Grisshammer: Eiweissumsatz und Ueberempfindlichkeit, Ztschr. f. exper. Path. u. Therap., 1912, x, 3, 412; Ueber den Einfluss parenteral verabreichter Proteinsubstanzen verschiedener Herkunft auf das Blutbild, ibid.

[4] Stäubli: Die klinische Bedeutung der Eosinophilie, Ergebn. d. inn. Med. u. Kinder., 1910, vi, 12; Ueber Eosinophilie, Samml. klin. Vortr., 1909, clxvii, 43.

[5] Herrick, W. W.: Experimental Eosinophilia with an Extract of an Animal Parasite: Its Relation to Anaphylaxis and Certain Clinical Problems, The Archives Int. Med., 1913, xi, 165.

[6] Ahl and Schittenhelm: Ueber experimentelle Eosinophilie nach parenteraler Zufer verschiedener Eiweissstoffe, Ztschr. f. d. ges. exper. Med., 1913, i, 111.

functions of these important cells offers at least the chance of illuminating the larger problem. It has been with this possibility in mind that the study of the effect of atropin on the eosinophils was undertaken.

Ehrlich, cited by Mayer,[7] has remarked that too little experimentation has been done on the relation of the eosinophils to chemical substances, and that the results thus far obtained have been inconstant because insufficient material has been used in such experimentation. In the present study of the influence of a chemical substance on the eosinophils it is thought that sufficient material has been used to meet this very appropriate objection.

Atropin was not selected at random; neither is the problem the narrow one that would at first thought appear. Auer[8] has recorded the observation that anaphylactic shock in guinea-pigs may be prevented by the injection of from 0.5 to 1 mg. of atropin. Since eosinophilia so constantly follows recovery from anaphylaxis, it is of interest to learn whether or not atropin influences the cellular reaction. Again, a clinical problem is concerned in the question of the control of the eosinophils by atropin. The term "eosinophil diathesis" has found its way into medical terminology. Under this heading are classified those persons prone to bronchial asthma, mucous colitis, urticarias and allied conditions that have as a frequent accompaniment an eosinophilia of the blood. Eppinger,[9] in a description of the somewhat vague clinical concept called "vagotonie," states that cases characterized by excessive functioning of the autonomic nervous system, "vagotonikers," show an excess of eosinophils in the circulating blood, which excess can be reduced by atropin. No experiments are cited in support of this statement. It has been suggested elsewhere that there is a relation between the problems of anaphylaxis, eosinophilia and that of bronchial asthma; that substances capable of influencing the eosinophil cell might be of clinical use in dealing with that baffling symptom asthma. With these questions in their somewhat complex relations in view, the study of the influence of atropin on the eosinophils was undertaken.

METHODS OF STUDY

Guinea-pigs were chosen for experiment for reasons sufficiently explained in numerous other communications by various writers.[10] The

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[7] Meyer: Die klinische Bedeutung der Eosinophilie, Berlin, S. Karger, 1905.

[8] Auer: The Effect of Vagus Section on Anaphylaxis in Guinea-Pigs, Jour. Exper. Med., 1910, xii, 638.

[9] Eppinger and Hess: Die Vagotonie, Samml. klin. Abhandl., 1910, Nos. 9 and 10, p. 41. Hopkins: A Clinical Study of Vagotonia, The Archives Int. Med., 1913, xii, 556.

[10] For discussion of the blood-picture and blood reactions of the guinea-pig the following may be consulted:

Opie: The Occurrence of Cells with Eosinophil Granulations, and Their Relation to Nutrition, Am. Jour. Med. Sc., 1904, cxxvii, 217; An Experiblood-counts were made by the method most commonly in use in clinical work. Blood was taken from the ear. The usual pipet giving a dilution of 1 : 10 was used to determine the total number of leukocytes, while for the differential count smears were made, stained by Wright's stain, and 200 cells counted with the oil-immersion lens. Several control counts were made before beginning each experiment. In all ten guinea-pigs were used. Atropin was given in a 10 per cent. solution by hypodermic injection. The horse-serum was given intraperitoneally. The dates of the blood-counts, and the amounts and times of administration of atropin and of serum are detailed in the accompanying charts, together with the curve illustrating the variations in total numbers of the eosinophil cells in a cubic millimeter of blood. The dosage of atropin was large, allowing for the tolerance to this drug shown by the graminivora.

PROTOCOLS OF EXPERIMENTS

EXPERIMENT 1.—Guinea-Pig 1 weighed 640 gm. Control counts showed constant eosinophilia, from 817 to 4,867 in a cubic millimeter. From June 27 to July 23 eleven doses of atropin sulphate, 0.002 gm., were given. From July 29 to August 13 ascending doses of from 0.04 to 0.15 gm. were given. Exact amounts

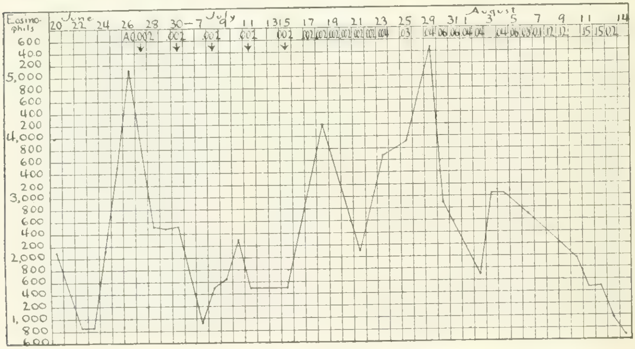

Chart 1.—Experiments on Guinea-Pig 1. In the charts the atropin dosage is given in grams, the figures preceded by the letter "A," and the serum is given in cubic centimeters, the figures preceded by the letter "S."

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mental Study of the Relation of Cells with Eosinophil Granulation to Infection with an Animal Parasite, ibid., 1904, cxxvii, 477.

Staubli: Trichinosis, 1909, p. 107 et seq.

Gulland and Goodall: The Blood, 1912, p. 76.

Kanthack and Hardy: Wandering Cells of Mammalia, Jour., Physiol., London, 1894, xvii, 81.

Herrick, W. W.: Footnote 5.

Klineberger and Karl: Die Blutmorphologie der Laboratoriumstiere, Leipsic, 1912.

and times of administration may be learned from Chart 1. There was definite fall in the eosinophil curve during the last ten days of the experiment, the period of administration of huge doses of atropin. At the same time there were toxic symptoms: loss of weight, roughening of the coat, weakness, loss of appetite, lessened activity, etc. Weight August 14, 592 gm.

Experiment 2.—Guinea-Pig 2 weighed 670 gm. Control counts showed eosinophils varying in numbers from 1,950 to 5,340. From June 30 to July 22, ten doses of atropin sulphate 0.002 gm., were given on alternate days without influence on the numbers of these cells. From July 23 to August 12, atropin sulphate in amounts from 0.04 to 0.15 gm. were given daily or every second day. No notable fall in the eosinophil curve was apparent. Toxic symptoms were produced of a character similar to those described in the case of Guinea-Pig 1. Weight August 13, 618 gm.

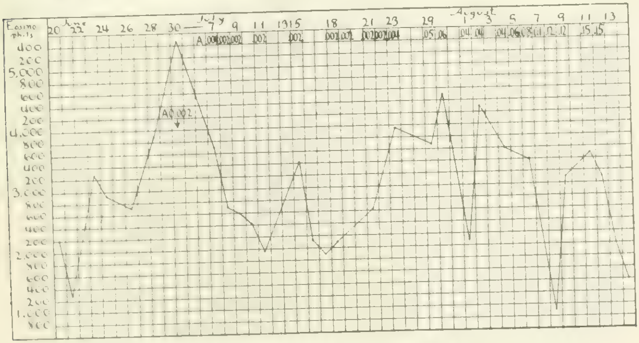

Chart 2.—Experiments on Guinea-Pig 2.

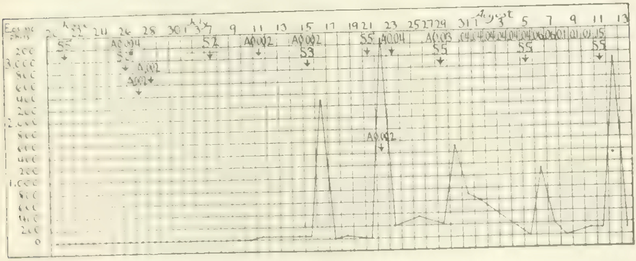

Chart 3.—Experiments on Guinea-Pig 3. * June 26, the serum was given one hour after the atropin.

Experiment 3.—Guinea-Pig 3 weighed 500 gm. During the control period no eosinophils were found in the circulating blood. Interval injections of serum after the third were followed by the usual eosinophilia. Atropin in large amounts, from 0.03 to 0.15 gm. on the day before that of the injection of serum apparently inhibited the rise in number of eosinophils in two instances, but in one instance did not prevent the development of a marked eosinophilia, which occurred despite daily injections of large amounts of atropin for a period of twelve days. The results in this instance are therefore contradictory.

Experiment 4.—Guinea-Pig 4 weighed 480 gm. The eosinophil response on the part of this animal to repeated injections of serum was slight though definitely present. This may have been due to the apparent general feebleness of the animal, which succumbed to a dose of atropin sulphate, 0.1 gm. Atropin given in doses of 0.002 or of .02 gm. at the time of administration of serum had no apparent effect on the subsequent rise in number of eosinophils.

Experiment 5.—Guinea-Pig 5 weighed 500 gm. This animal was used as a control to show the effect of interval injections of serum on the eosinophils. Atropin sulphate, 0.04 gm., given at the time of the sixth inoculation of serum, apparently exerted an inhibitory influence on the subsequent eosinophilia. This eosinophilia, though present, was much less than in the two preceding instances following inoculation of serum alone, and may possibly have been a result of the action of atropin.

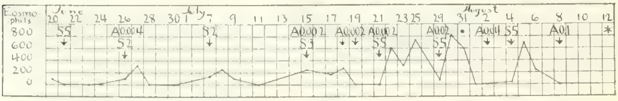

Chart 4.—Experiments on Guinea-Pig 4. * Ill, weak, died.

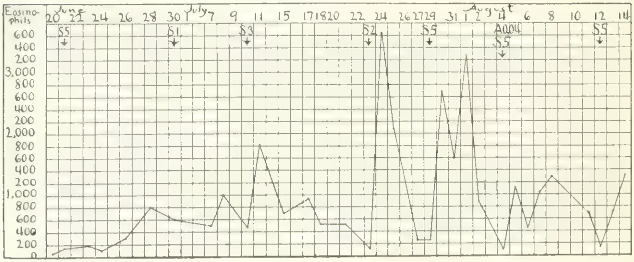

Chart 5.—Experiments on Guinea-Pig 5.

Experiment 6.—Guinea-Pig 6 weighed 480 gm. Control counts of eosinophils showed from 270 to 648. Three injections of serum alone at intervals of from seven to twelve days were followed in case of the last two by increase of eosinophils, the maximum number being 4,638. July 29, atropin sulphate, 0.02 gm., with serum, 5 c.c., was injected. There was response on the part of the eosinophils, their numbers rising from 836 to 2,362 forty-eight hours later. August 4, atropin, 0.04 gm., was injected. August 5, serum, 5 c.c., was injected. Eosinophils, absent on the 5th, rose to 1,120 the 6th, a much lower figure than that seen after other injections of serum alone in this animal. August 11, eosinophils were 576. Atropin, 0.1 gm. was injected. August 12, eosinophils were 1,581. Serum, 5 c.c. was injected. August 14, eosinophils were 864. In this instance the usual rise in the number of eosinophils was lacking.

Experiment 7.—Guinea-Pig 7 weighed 500 gm. In this animal enormous and finally lethal doses of atropin did not prevent the development of the eosinophilia consequent on the interval injections of serum, such an eosinophilia being present on the day of death.

Experiment 8.—Guinea-Pig 8 weighed 560 gm. Control counts showed a moderately high eosinophilia, averaging 1,300 in a cubic millimeter. Atropin sulphate, 0.05 gm., was given twice daily from December 1 to 9. On the latter date a single dose of 0.1 gm. was given. From November 15 to December 9 four interval injections of serum, 5 c.c., were given, the last injection being followed within two minutes by convulsions and death. It is of interest that

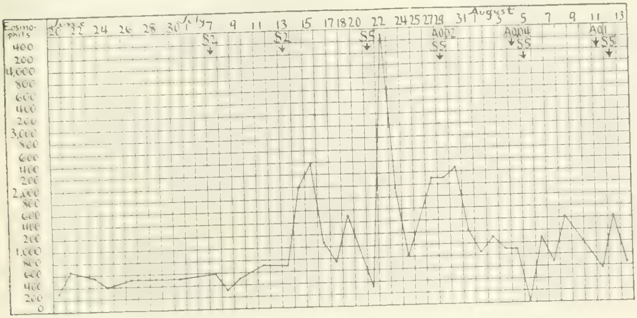

Chart 6.—Experiments on Guinea-Pig 6.

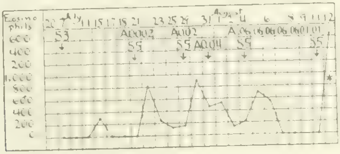

Chart 7.—Experiments on Guinea-Pig 7. * Died.

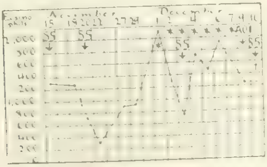

Chart 8.—Experiments on Guinea-Pig 8. * Atropin sulphate, 0.05 gm. twice daily. † Death in two minutes from convulsions.

the large amounts of atropin administered before the fatal injection of serum did not prevent the development of an apparent acute anaphylaxis. The injections of serum were not followed by any notable rise in the number of eosinophils. Throughout the period of administration of atropin and serum the average level of the eosinophil curve remained about as during the control period. December 8 the weight was 543 gm.

Experiment 9.—Guinea-Pig 9 weighed 521 gm. Control counts showed constant eosinophilia, these cells numbering from 1,000 to 2,000 in a cubic millimeter. Serum, 5 c.c., was given November 15. This was repeated November 20 and was followed by a pronounced rise in eosinophils to 1,825. Atropin, 0.05 gm., was given twice daily from December 1. Serum, 3 c.c., was given December 3 without subsequent eosinophilia. December 10, serum, 5 c.c., was injected. No eosinophilia followed, and on December 11 and the following days these cells diminished in number. A fifth injection of serum, December 16, was followed by a very slight rise in the eosinophils, from zero to 500. In this instance there was definite effect on the eosinophils, the diminution in their numbers after the administration of atropin being constant and striking. The animal showed toxic symptoms and lost weight to 493 gm.

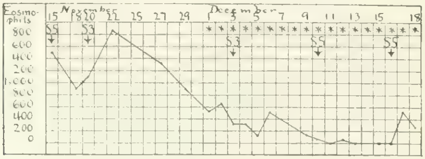

Chart 9.—Experiments on Guinea-Pig 9. * Atropin sulphate, 0.05 gm. twice daily.

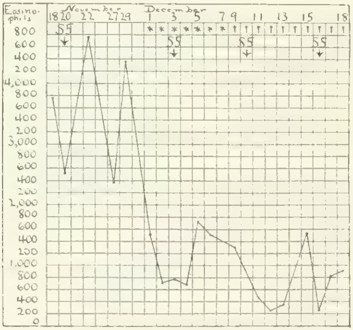

Chart 10.—Experiments on Guinea-Pig 10. * Atropin sulphate, 0.05 gm. twice daily. † Atropin sulphate 0.1 gm. twice daily.

Experiment 10.—Guinea-Pig 10 weighed 522 gm. Control counts of eosinophils were high—from 2,400 to 4,800. From December 1, atropin, 0.5 gm., was given twice daily. After this date the eosinophils at no time numbered more than 1,700. From December 9 the amount of atropin given was doubled, 0.1 gm. being the dose administered. Following this the eosinophil count fell to 200, and remained constantly low. Interval injections of serum resulted in no significant eosinophilic increase; in fact, in one instance a fall followed such an injection. The effect of atropin seems definite in the case of this animal. There were toxic symptoms and loss of weight to 490 gm.

REVIEW OF EXPERIMENTS

Review of the experiments detailed above brings out the fact that definite fall in the number of eosinophils followed administration of atropin in but two of ten animals. The animals in which such positive result was obtained were two of three receiving large doses of atropin, from 0.05 to 0.1 gm., every twelve hours (Guinea-Pigs 9 and 10). The third animal receiving such doses showed no effect on the eosinophils (Guinea-Pig 8). This guinea-pig, however, died from anaphylaxis before a sufficient period of observation had elapsed to make conclusions of value. A less definite result was seen in Guinea-Pig 1. This animal received daily doses of atropin from 0.03 to 0.2 gm., and showed considerable reduction in the number of eosinophil cells from the high average found throughout the earlier part of the period of observation. Guinea-Pig 2, on the same dosage of atropin, showed little change in number of eosinophils. The smaller doses of atropin, from 0.002 to 0.004 gm., were without influence on the eosinophil content of the blood. In order, therefore, to reduce a high eosinophilia with atropin, very large doses sufficient to cause toxic symptoms must be given at frequent intervals.

INFLUENCE OF ATROPIN ON THE EOSINOPHILIA FOLLOWING INJECTION OF SERUM

Atropin given with, immediately before or twenty-four hours before the interval injection of serum, seemed to inhibit to some degree the subsequent rise in number of the eosinophils (Guinea-Pigs 3, 5, 6, 9 and 10); such rise being absent or less than that occurring in the same animal after injections of serum without atropin. This result is not constant. For exceptions observe Charts 3, 4 and 7. In animals receiving large doses of atropin at intervals of twelve hours, eosinophilic response was slight or lacking (Guinea-Pigs 8, 9 and 10). Frequently there was a drop in the curve of these cells after such injections—a most exceptional occurrence under ordinary conditions.

DISCUSSION OF RESULTS

It seems clear that the mechanism by which the number of eosinophils in the circulating blood of guinea-pigs is increased is not influenced by ordinary amounts of atropin. This mechanism, however, may be depressed or paralyzed by excessive doses of the drug, when such doses are given as often as every twelve hours.

The method of action of atropin in this connection is obscure and involves the question of the general control of leukocytes, which is far from solution. One can only speculate as to the possible influence of atropin on chemotaxis, or as to an altogether hypothetical influence of the autonomic nervous system on bone-marrow activity which is inhibited by the alkaloid; or one may, perhaps with more reason, consider that the results noted are due to a general interference with a highly specialized function by a strong poison and not to any more specific influence. In connection with the latter conception, Opie's demonstration of the close relation of the number of eosinophils of guinea-pigs to their nutrition is important. Opie[10] found that in guinea-pigs in which there was loss in weight from starvation or other cause the eosinophil cells were regularly much reduced in number. In the present study the nutrition of the animals suffered from the large doses of atropin. Loss of weight and appetite, roughening of the coat, lessened activity, etc., were noted in all animals showing reduction in numbers of eosinophils or lack of response on the part of these cells to serum injections. It may therefore be reasonable to consider the effect of atropin on the eosinophils here observed an indirect one and a result of disturbed nutrition from large doses of a poisonous alkaloid.

There is strong objection to applying by analogy to man conclusions gained by experiments on an animal like the guinea-pig, particularly with atropin, a poison to which the animal is, as compared to man, relatively tolerant. The very large doses of atropin given, however, and the fact that the blood reactions of the guinea-pig are strikingly like those of man, must have weight. Clinically it has never been possible in my experience notably to reduce a hypereosinophilia by atropin in ordinary doses. Animal experimentation seems to lend some degree of corroboration to this clinical experience.

CONCLUSIONS

Atropin in ordinary, non-toxic doses has no striking influence on the eosinophil cells of the guinea-pig's blood.

Given in toxic doses resulting in loss in weight and other signs of disturbed nutrition, and particularly when such doses are repeated as often as every twelve hours, there is a diminution in the number of these cells, and the eosinophilia following interval injections of serum is diminished or absent.

It is probable that this effect of atropin is not specific, but is the depression of a highly specialized function by the general effect on nutrition of large amounts of a strong poison.

CLINICAL OBSERVATIONS ON DEFECTIVE CONDUCTION IN THE BRANCHES OF THE AURICULO-VENTRICULAR BUNDLE *

A REPORT OF TWENTY-TWO CASES, IN WHICH ABERRANT BEATS WERE OBTAINED

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CLEVELAND, O.

The present communication is based on material collected in the Cardiographic Department of University College Hospital Medical School, London. It includes a description of twenty-two cases in which evidence of defective conduction in one or the other branch of the auriculoventricular bundle was observed electrocardiographically, a description of the characteristic features of aberrant curves and remarks on the clinical associations of the corresponding defects.

As defective conductivity of the main stem of the auriculoventricular bundle gives rise to a characteristic electrocardiogram, so do lesions of its individual branches give rise to abnormal electrocardiographic curves, which, within certain limits, follow definite types. It is with these definitely known forms of abnormal curves that we are concerned.

As *aberrant*[1] are grouped those heart-beats which result as a direct sequence of impulses which arise in a supraventricular focus, but which reach the ventricle either through an unusual route or through normal but partially defective channels. In either case the resulting electrocardiograms will show conspicuous differences from the normal, differences which depend either on a permanent organic lesion, or, less commonly, on a temporary defect in conductivity.

By supraventricular focus is meant a focus in the auricle or junctional tissues above the division of the main stem of the bundle. The impulses giving rise to the independent ventricular rhythm of complete heart-block are of supraventricular origin, for they arise in the main bundle, and so, as we shall see, aberrant types of ventricular contraction may be associated with complete dissociation.

It has been shown by Eppinger and Rothberger[2] that experimental lesions of the branches of the auriculoventricular bundle are followed by characteristic electrocardiographic curves, that a lesion of the right

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* Submitted for publication Feb. 19, 1914.

[1] Lewis: Heart, 1912, iii, 293.

[2] Eppinger and Rothberger: Ztschr. f. klin. Med., 1910, lxx, 1.

branch of the auriculoventricular bundle gives rise, in Lead II (Rt.A.—Lt.L.), to an electrocardiogram which resembles that obtained on stimulation of the left and apical portion of the ventricle, the initial deflection of the ventricular complex being directed downward (apex negative); while a lesion of the left branch of the auriculoventricular bundle gives rise to the reverse picture, an electrocardiogram resembling that obtained on stimulation of the right and basal portion of the ventricle, the initial deflection of the ventricular complex being directed upward (base negative).

In either instance the resulting electrocardiogram is essentially diphasic, and, although always preceded by an auricular complex, the ventricular complexes resemble those known to occur as the result of intrinsic premature ventricular contractions, as shown by the prolongation of the period covering the opening phases, by the increase in amplitude and direction of the initial deflection in the several leads. Soon this experimental evidence was further established by Eppinger and Stoerk,[3] who were able, in two clinical instances by subsequent post-mortem examination, to confirm the diagnosis made from electrocardiograms of a lesion of the right branch of the auriculoventricular bundle.

More recent clinical and electrocardiographic evidence has confirmed these earlier observations, a number of workers having reported in detail cases associated with lesions of one or the other branch of the auriculoventricular bundle, in some of which the diagnosis has been confirmed by histological examination.

Cohn and Lewis[4] report a most unusual case of auricular fibrillation and heart-block, in which it was shown by a histological examination that both branches of the auriculoventricular bundle had been destroyed. The electrocardiograms obtained from this case were practically identical with the curves obtained from a similar experimental lesion by Eppinger and Rothberger.

Lewis[5] has published a report of a unique case illustrating a temporary defect in conductivity of the right branch of the auriculoventricular bundle, the records of which are included in the present series (Case 12).

Mathewson[6] has recently reported four cases associated with lesions of one or the other branch of the auriculoventricular bundle.

In the light of the accumulated observations it has seemed possible to attempt to classify in greater detail the aberrant curves resulting from lesions of the branches of the auriculoventricular bundle.

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[3] Eppinger and Stoerk: Ztschr. f. klin. Med., 1910, lxx, 157.

[4] Cohn and Lewis: Heart, 1912, iv, 15.

[5] Lewis: Brit. Med. Jour., 1913, i, 484.

[6] Mathewson: Heart, 1913, iv, 385.

DISTINCTIONS BETWEEN PHYSIOLOGICAL AND ABERRANT TYPES OF CURVE

In order to bring out more clearly the essential distinctions between the normal and the aberrant electrocardiogram, I summarize in tabular form the chief points of difference between them and physiological electrocardiograms. It must be borne in mind, however, that, though we are dealing with an aberrant type of electric curve, the ventricular contractions were of supraventricular origin, each ventricular beat being preceded by an auricular contraction—except in one case of complete heart-block—and that the resulting ventricular complexes alone are abnormal.

In the accompanying figures all three leads have been employed, as it is possible to arrive at accurate conclusions only by an analysis of the curves obtained from the three leads. In Lead II, in the presence of lesions of the branches of the auriculoventricular bundle, the initial deflection of the ventricular complex usually follows the direction of the corresponding deflection in Lead III, but there are exceptions to this rule.

TABLE 1.—Contrasts Between Normal and Aberrant Electrocardiograms

NORMAL	ABERRANT
1. Supraventricular complex. Presence of auricular or P summits.	1. Supraventricular complex. Presence of auricular or P summits.
2. P-R interval .13 to .18 second, never more than 0.2 second.	2. P-R interval frequently prolonged beyond 0.2 second.
3. Q-R-S interval less than 0.1 second, and less than one-third of entire complex.	3. Q-R-S interval exceeds 0.1 second and as a rule constitutes more than one-third of the entire complex.
4. Relatively small amplitude of initial deflections.	4. Relatively increased amplitude of initial deflections.
5. Final deflection T upright and in the same direction as the most prominent deflection (R) in Leads I and II, and usually in Lead III.	5. Final deflection T' usually in a direction opposite to that of the prominent initial deflection. May be upright or inverted.
6. Initial deflections as a rule unnotched.	6. Initial deflections almost always show notching in one lead at least. Many bizarre forms seen.
7. Final deflection T as a rule plainly to be seen, but not exaggerated.	7. Final deflection T' frequently much exaggerated.

Thus it will be seen that the differences between the normal and the aberrant electrocardiogram consist essentially in the longer duration of the opening phases, in the greatly increased amplitude of the initial deflections, in the notching of R' and S' so often seen in the aberrant curves—the initial deflections are spoken of as R' and S', to distinguish them from the deflections R and S of the normal curve—and in the generally diphasic character of the aberrant curve, especially in Leads I and III, while the normal electrocardiogram is triphasic or quadriphasic.

Whatever the location of the lesion, whether involving the right or the left branch of the auriculoventricular bundle, the prominent initial deflections are always in *opposite* directions in Leads I and III. This rule, while constant for R' and S', usually holds for the final deflection T', which, as has been stated, commonly lies in a direction opposite to the prominent initial deflections R' and S', and is usually conspicuous.

Figure 8 illustrates in detail the distinguishing characteristics of the aberrant electrocardiogram; it is an instance of temporary defect in the conductivity of the right branch of the auriculoventricular bundle, associated with relative left ventricular hypertrophy. The greatly increased duration and amplitude of the initial deflections is at once apparent. The *P-R* interval measures 0.18 sec. The *Q-R-S* interval measures more than 0.1 sec. The conspicuous initial deflections R' and S' in Leads I and III are seen to be in opposite directions. The initial deflection S' in Lead II follows the same direction as the corresponding deflection in Lead III. The final deflection T' is in a direction opposite to the conspicuous initial deflection in all leads, being inverted in Lead I, and upright in Leads II and III. The notching of R' in Lead I and of S' in Leads II and III is apparent. The final deflection T' is much exaggerated.

DISTINGUISHING POINTS BETWEEN THE ABERRANT ELECTROCARDIOGRAM AND THAT OBTAINED AS A RESULT OF CARDIAC HYPERTROPHY

While it is freely admitted that the attempt to correlate certain types of electrocardiogram with a definite form of cardiac hypertrophy may need subsequent revision, it has been shown that in the presence of specific valve-lesions, commonly associated with preponderating hypertrophy of the left or right ventricle, distinctive electrocardiograms have been obtained, controlled in a small number of instances by subsequent post-mortem examination.[7]

It may, therefore, be stated that the electrocardiographic curves obtained as a result of cardiac hypertrophy, from whatever cause, depend essentially on the degree and distribution of the hypertrophy present in a given case, whether left or right side predominates.

In the presence of left ventricular preponderance the resulting electrocardiogram is characterized by a tall, conspicuous initial deflection R in Lead I, with an inconspicuous S, and by a deep deflection S, with an inconspicuous R, in Lead III. Lead II is less characteristic.

In the presence of right ventricular preponderance the picture is reversed. In Lead I, R is inconspicuous, the initial deflection S appearing as a deep depression, while in Lead III, R appears as a tall conspicuous peak, and S is small.

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[7] Lewis: Clinical Electrocardiography, London, 1913, p. 24.

It is apparent that, as in the aberrant electrocardiogram, the most prominent initial deflections in Leads I and III are in opposite directions, the direction depending on the predominance of one or the other ventricle. The electrocardiogram obtained from a case of simple cardiac hypertrophy may be distinguished from the aberrant type, which it resembles in many respects, by the shorter duration of the opening phases of the complex, by the lesser amplitude of the prominent deflections, by the direction of the deflection T in relation to the deflections R and S, by the absence of notching of R and S, and by the normal triphasic or quadriphasic character of the complex. In aberrant curves T' is in the opposite direction to the main initial deflection (R' or S') in Leads I and III; in the curves of hypertrophy T and R or S are often in the same direction in these leads.

When, as occasionally happens, a temporary defect in conductivity occurs in the course of an acute breakdown of an already hypertrophied heart, a condition almost always present in these cases, one may be able to compare the aberrant curve obtained from such a heart with the curve of simple hypertrophy obtained later, after the disappearance of the transient functional defect.

Such instances are not common, but the occurrence of a transient aberrant electrocardiogram is most important from the point of view of a comparison of the aberrant curve with the physiological type in the same case.

Allusion has been made to the single instance of such temporary defect in conductivity included in this series; and the facts stated above are well illustrated by a comparison of Figures 8 and 9, which accompany Case 12, the bizarre aberrant electrocardiogram resulting from the acute lesion of the right branch of the bundle, giving place, on the subsidence of the acute process, to the physiological electrocardiogram recorded on the following day.

No change could be more marked: the earlier curve due to defective conduction plus left ventricular preponderance, the latter essentially the curve of simple cardiac hypertrophy. No more striking evidence than these two figures could be offered that the aberrant electrocardiogram does not depend on the presence of cardiac hypertrophy.

In this connection reference may also be made to Case 20, Figures 16 and 17. Here we are fortunate in having obtained the physiological electrocardiogram of the individual, before the development of defective conductivity, for comparison with the curves obtained later and after the development of the lesion involving the right branch. The difference between the two figures is apparent at a glance: the earlier physiological electrocardiogram could not by any possible chance be confused with the aberrant complex obtained later, after the development of defective conductivity.

SIDE OF THE DEFECT

In the twenty-two cases of this series the right branch of the auriculoventricular bundle has been involved in twenty-one, the left branch in but one instance. The majority of previously described cases also are those in which a defect of the right branch has been diagnosed.

TABLE 2.—Summary of Cardiograms in Cases 1 to 22 *

Patient	Case No.	Fig. No.	*P-R* Interval Seconds
D. B.	1	......	0.13.
G. S.	2	......	0.24.
J. P.	3	......	A. F.
H. C.	4	1	0.20.
J. P.	5	2	A. F.
R. S.	6	......	0.34 (1-17-11).
			0.30 (8-7-12).
			C. H. B. (11-3-12).
			Dropped beats (11-13-12).
		3	Dropped beats (2-6-13).
		......	C. H. B. (11-24-13).
W. S.	7	4	0.21 (three observations).
H. C.	8	......	0.29.
S. R.	9	5	0.17-0.18.
R. B.	10	6	0.21-0.23 (four observations).
C. H.	11	......	0.26 (6-12-12).
			0.16 (7-12-12).
		7	0.20 (7-25-12).
W. C.	12	8	0.18 (8-18-12).
		9	0.18 (8-19-12).
		......	0.20 (10-6-12).
R. A.	13	10	0.13.
W. P.	14	......	A. F.
J. W.	15	11	0.20.
D. E.	16	12	0.14.
W. O.	17	......	0.28 (2-17-13).
		13	0.17 (5-12-13).
G. C.	18	14	0.20.
W. J.	19	15	0.18-0.20 (two observations).
D. H.	20	16	0.30 (2-27-13).
			0.24 (3-5-13).
			0.24 (4-7-13).
			0.21 (4-10-13).
			0.24 (4-28-13).
		17	0.22 (5-5-13).
		......	0.29 (5-15-13).
J. M.	21	18	0.17.
E. N.	22	19	C. H. B.

* The conditions found in Cases 1 to 22 are as follows: Aortic disease, 7, 9, 10, 11, 17, 18, 20, 21; varying degrees of heart-block, 2, 4, 6, 7, 8, 10, 11, 12, 15, 17, 18, 20, 22; Cheyne-Stokes respiration, 2, 3, 5, 16; auricular fibrillation, 3, 5, 14; various other associated pathological states, 1, 4, 8, 13, 15, 19, 22. Subsequent histories are: Dead, Patients 2, 3, 5, 7, 9, 10, 11, 14, 16, 18, 19, 20; alive (condition precarious) 8, 12, 13, 17, 21, 22; alive (condition not precarious) 1 and 4; history unknown (condition precarious when last seen) 6 and 15.

There is no entirely satisfactory explanation of this difference in incidence. It is possible, however, that the predominance of the right-side lesion may be explained on anatomical grounds, the right branch, as a circumscribed track, being by far the longer.

Table 2 summarizes the cases reported in detail. In the column giving the *P-R* intervals, these have been grouped in chronological order; otherwise, so far as is possible, wholly on the basis of the associated pathological condition.

RELATION TO AURICULOVENTRICULAR BLOCK

Deficiency in the conduction of the branches of the bundle has a close relation to a similar deficiency in the main stem of the auriculoventricular trunk. It has been emphasized by several writers, Sternberg[8] and Monckeberg[9] among others, that the conducting tissues which unite the auricles and ventricles have a more or less special pathology. Aschoff[10] has called attention to their liability to damage from small hemorrhages, as a result of their curious sheathing with connective tissue; and it is known that fatty degeneration falls unequally on the conducting tissues and the rest of the muscle of auricle and ventricle. Aschoff[11] and Butterfield[12] have shown that the infiltration in rheumatic carditis is observed in the subendocardial tissues and that it is especially prone to invade the conjunctional tissues. That the conducting tissues have a special physiology is certain, for their glycogen content is known to be much greater than that of ordinary cardiac muscle (Nagayo[13]).

Dealing with the same question from a purely clinical point of view the facts point clearly in the same direction. The normal human *P-R* interval usually varies between 0.13 and 0.18 seconds; a higher value than 0.18 is very exceptional; the commonest values are from 0.13 to 0.16 seconds, as shown by Lewis and Gilder.[14] In the present series of twenty-two cases, a sequential rhythm has been present in eighteen. In thirteen of these eighteen cases the *P-R* interval was prolonged, constantly or on occasion. In four (Cases 6, 12, 17 and 20) it showed considerable variation. One of these (Case 6) showed auriculoventricular heart-block of extraordinarily varying degree, namely, simple prolongation of the interval, dropped beats and complete dissociation. In another of the series (Case 22) complete dissociation was a constant feature.

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[8] Sternberg: Verhandl. d. deutsch. path. Gesellsch., 1910, xiv, 102.

[9] Monckeberg: Verhandl. d. deutsch. path. Gesellsch., 1912, xvi, 460.

[10] Aschoff: Verhandl. d. deutsch. path. Gesellsch., 1910, xiv, 3.

[11] Aschoff: Brit. Med. Jour., 1906, ii, 1103.

[12] Butterfield: Heart, 1912, iii, 203.

[13] Nagayo: Verhandl. d. deutsch. path. Gesellsch., 1908, xii, 150.

[14] Lewis and Gilder: Phil. Tr. Roy. Soc., 1912, ccii, 351.

This clinical evidence speaks very strongly for the frequency of functional damage of the conducting tissues as a whole, though necessarily the damage varies in extent in different parts of the system from case to case. In many of the published cases of complete heart-block, trunk-branch lesions are demonstrated by the electrocardiographic curves.[15]

Experimental evidence points in the same direction; Lewis and Mathison[16] have shown that asphyxia of cats produces auriculoventricular heart-block, and that at the same time it frequently damages the conduction in the main branches of the auriculoventricular system.

We have every reason to conclude, from the evidence derived from all sources, that inflammatory lesions and invasions of the heart by poisons may act in a more or less specific manner, picking out the special system of muscle fibers which unite the auricle and ventricle. The physiology and the pathology of these tissues is largely a special physiology and pathology.

RELATION TO AORTIC VALVE DISEASE

It is a remarkable fact that out of the present series of twenty-two cases, eight patients have exhibited well-developed aortic valve lesions. The frequent association of damage of the branches of the auriculoventricular bundle with aortic valve disease can not be regarded as purely accidental. Yet the association meets with no very plausible explanation; especially so because in each of the eight cases the right trunk was defective. Lesions of the aortic valve would be expected, *a priori,* in association with lesions involving the conductivity of the left branch, for the bases of the valves are in close proximity to it. Nevertheless this association does not occur. Too much emphasis may be laid on this argument; it is weakened by a knowledge of the relative frequency of lesions of the right and left trunk-branches; the former are far commoner. In the present series the right branch was defective in twenty-one cases, the left in one only.

An explanation that the curves are in reality but an expression of left-side muscular preponderance does not suffice. It is perfectly true that the curves of the aberrant type, associated with right-branch lesions, and those speaking for left-side preponderance resemble each other; but there are, nevertheless, clear and recognizable distinctions between them, distinctions which have been emphasized already and which are to be seen in the curves of Cases 12 and 20.

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[15] See the case reported by Cohn and Lewis, already referred to, and the second case of Mathewson's series, to which reference has been made.

[16] Lewis and Mathison: Heart, 1910, ii, 47.

We are able to produce very satisfactory evidence that the curves in question are not those of left-side preponderance pure and simple, for in these two instances the physiological electrocardiograms for the particular individuals have been obtained for comparison. In Case 12, the change in the type of electrocardiogram is profound and sudden; the aberrant type of curve (Fig. 8) could not result purely from hypertrophy, when within a day an entirely different and more normal type of curve is displayed (Fig. 9). The reason for the frequent association of aberrant curves with aortic valve disease is, therefore, still obscure.

RELATION TO EXTRASYSTOLES

The common occurrence of extrasystoles in conjunction with aberrant forms of electrocardiograms suggests that the lesion which produces the conduction defect may also awaken the new impulses; this the more, since it has been suggested that extrasystoles are often of bundle or bundle-branch origin. It is necessary to examine the direction of the deflections from this point of view. Our curves give us only meager information. Though extrasystoles were seen in a much larger proportion of the cases, the curves in our possession show them in seven instances only. We consider Leads I and III as of most importance from our present point of view. The aberrant curves are mainly diphasic; the curves due to extrasystoles are also mainly diphasic, but in a given case the deflections of the diphasic complexes are usually in opposite directions when aberrant and extrasystolic curves are compared (Table II).

That is to say, in most cases the extrasystole arises in the ventricle opposite to that in which the aberrant beat originates. This is what would be expected if a lesion produced defective conduction in the branch, and also provoked extrasystoles from it. Thus in Cases 10, 14 and 22 the extrasystoles arose from the right or basal portion of the heart, as shown by all leads. In Case 3 the extrasystoles were, on the other hand, from the left and apical portion of the ventricle. In the remaining Cases 11, 15, 20, the deflections of the extrasystole were opposite to those of the aberrant curve in one lead (Lead II), but in the same direction in another lead (Lead I or Lead III).

RELATION TO PROGNOSIS

The prognostic value of any given sign in disease of the heart is always a difficult problem. Especially is this the case when the sign is frequently associated with other signs of a grave nature.

An organic lesion confined to one branch of the auriculoventricular bundle is hardly one which can be regarded as jeopardizing life. We find that a bundle-branch lesion may be present for many years and the heart still show general efficiency (Cases 1 and 4). But just as lesions of the branches are rarely confined to the branches, but are associated with defects in the main bundle, so too the defects are probably but rarely confined to the conducting system, but spread beyond it into the general musculature to a lesser or greater extent.

From analogy with auriculoventricular heart-block, we must regard a bundle-branch lesion as significant of an invasion of the heart-muscle, be it acute or chronic, and therefore of considerable gravity in most instances. In the present series of cases, the gravity of such a lesion is well illustrated. In twenty-two cases, reports of which have been collected within a few years, twelve patients are known to have died (Patients 2, 3, 5, 7, 9, 10, 11, 14, 16, 18, 19, 20). Six are alive but known to be in a precarious condition (Patients 8, 12, 13, 17, 21, 22); two have been lost sight of, but were in a precarious condition when last seen (Patients 6 and 15). Two only (Patients 1 and 4) have been under observation for considerable periods and show no signs of increasing heart-failure.

TABLE 3.—Summary of Cardiograms in Cases 1 to 22 Showing Occurrence of Premature Beats *

Case No.	Direction in Relation to Initial Deflections	Lead
3	Same	I, III
10	Opposite	I, II, III
11	Opposite	II
11	Same	III
14	Opposite	I, II, III
15	Same	III
20	Opposite	II
20	Same	I
22	Opposite	I. III

* In cases 2, 16, 17, 21, premature beats were present, but were not recorded electrocardiographically.

The frequent association of the condition with alternation of the heart, auricular fibrillation (Cases 3, 5, 14), Cheyne-Stokes respiration (Cases 2, 3, 5, 16), great enlargement of the heart and signs of circulatory embarrassment is in itself significant.

REPORT OF CASES

Case 1.—*Myocarditis, fibrosis of the left lung with bronchiectasis.*

Patient.—D. B., a girl, aged 16, was admitted to the hospital during the year 1906, complaining of cough, shortness or breath and pain in the left side of the chest.

Family History.—A sister has had rheumatic fever. Her father died of pneumonia complicated by "heart disease."

Personal History.—A delicate child at birth, the patient has had a cough all her life; though it has become much more troublesome of late. She has had no acute illnesses. There is no history of rheumatic fever or chorea. The shortness of breath, especially prominent on exertion, and the pain in the chest are recent developments. She brings up a little yellow sputum.

Condition on Admission.—The patient is poorly developed, with a certain degree of scoliosis, the curvature being toward the left side. The color of the cheeks is heightened. There is impairment of resonance over the whole left side of the chest both in front and behind; the capacity of this side is diminished. In the left intrascapular region the breath-sounds are tubular and bronchophony and pectoriloquy are heard; coarse clicking râles are audible over the same region, some of which synchronize with the heart-beats. A little purulent sputum contained no tubercle bacilli. The respirations are normal.

Heart.—Pulsation is seen over almost the whole left chest in front. The point of maximum impulse is diffuse in the sixth interspace near the posterior axillary line; posteriorly it is thrusting in character. A diastolic thrill is felt over the apex region. The cardiac dulness extends from the third rib above, and from the left margin of the sternum to the posterior axillary line. Systolic and diastolic murmurs are heard at the apex. A harsh systolic murmur is present at the aortic cartilage. The pulse is 76 to the minute and regular; the arteries are soft. There are no signs of venous engorgement or of dropsy. The urine contains no albumin.

Condition on Readmission (Nov. 9, 1912).—After six years the patient has been readmitted for the same symptoms. Pain has been present for twelve months, and shortness of breath, which has never entirely abated, is more distressing. From time to time she brings up large quantities of sputum. The physical signs at this time are very similar to those previously observed. The signs over the fibrosed lung are almost unaltered. The limits of cardiac dulness are the same. The murmurs remain unchanged. The respirations are not increased; there is but little venous engorgement; dropsy is absent; the urine contains no albumin. The temperature never rises above 99 F.

Electrocardiograms.—The P-R interval measured 0.13 second. In Leads I and II the initial deflection was abrupt and notched, having a total duration of 0.1 second. In Lead III an upward phase was succeeded by a larger downward phase; the two together measuring 0.1 second.

Subsequent History (June 21, 1913).—The patient is alive and in fair condition.

CASE 2.—*Myocarditis, extrasystoles, alternation, Cheyne-Stokes breathing and death.*

Patient.—G. S., a business man, aged 63, was first seen April 27, 1910, complaining of cough and shortness of breath on exertion.

Personal History.—With the exception of occasional attacks of gout the patient has had no illness since his boyhood. He has complained of his present symptoms for the past five months; these consist chiefly of an irritating cough, which is accompanied by considerable shortness of breath.

Condition on Admission.—The patient is well developed and shows no sign of cyanosis. He has Cheyne-Stokes breathing.

Heart.—The cardiac dulness extends two inches to the left of the nipple line. The first sound at the apex is reduplicated. There are no murmurs. The pulse is full and intermits from time to time. The blood-pressure is 125 mm. Hg.

Graphic Records.—Polygraphic records showed that the intermissions of the pulse were the result of premature contractions of the ventricle. These are followed by alternation. The *a-c* interval is distinctly prolonged.

Subsequent History.—The patient died twelve months later.

Electrocardiograms.—The P-R interval measured 0.24 second. The ventricular curves were similar to those shown in Figure 8.

CASE 3.—*Rheumatic myocarditis, high blood-pressure, auricular fibrillation, alternation, Cheyne-Stokes breathing, nephritis, urethral stricture; gradual failure and death.*

Patient.—J. P., a shop-keeper, aged 65, was admitted to the hospital Aug. 1, 1911, complaining of shortness of breath, pain in the chest, loss in weight and sleeplessness.

Personal History.—At the age of 26, 32 and 48 the patient had rheumatic fever. At 59 he had a slight "apoplectic stroke" and lost the sight of his left eye. He has been treated for urethral stricture for eighteen years.

Present Illness.—The patient states that twelve months ago he was quite free from any discomfort. About this time he began to suffer from shortness of breath, which has steadily increased; at present the slightest exertion brings it on. He has experienced shooting pains in the left side of the chest, and also, from time to time, in the right hypochondrium. The breathing is said to be heavy and periodic at night. He has lost 42 pounds in weight. He sleeps but two or three hours each night. His appetite is poor.

Condition on Admission.—The patient is well nourished and cyanotic and exhibits conspicuous Cheyne-Stokes breathing. The liver is palpable and tender an inch below the costal margin. There is slight edema of the legs and some ascites present. The specific gravity of the urine ranges from 1.010 to 1.016; albumin, sugar and pus are present in excess. The pulse is very irregular, the rate being 90 to 120 per minute; the arteries seem but little thickened. Most of the pulse beats pass a cuff-pressure of 200 mm. Hg.

Heart.—The apex-beat is not visible; the limits of cardiac dulness lie 2 inches to the right and 5 to the left of the midsternal line. The heart-sounds are clear, but very irregular; there are no murmurs.

Course of Disease.—The patient remained in the hospital for some weeks and improved a good deal in health. He passed from observation, but his wife wrote subsequently to say that he gradually became weaker, thinner and more short of breath. Dec. 5, 1911, when sitting up in a chair, he asked to be put to bed again, but almost immediately he became relaxed and died.

Electrocardiograms.—The P-R interval could not be determined, owing to the constant presence of auricular fibrillation. The ventricular complexes were similar to those shown in Figure 6. The extraventricular systoles recorded arose from the left and apical portion of the heart, being in the same direction as the initial deflections R' and S' in Leads I and III.

CASE 4.—*Pericarditis with effusion, arhythmia, drainage of the pericardium and recovery.* (Electrocardiograms, Fig. 1.)

Patient.—H. C., a woodcarver, aged 28, was admitted to the hospital Aug. 8, 1911, complaing of indigestion and palpitation of the heart.

Family History.—Negative.

Personal History.—The patient had pneumonia as a child and so-called "muscular rheumatism" two years ago. There is no history of rheumatic fever or chorea. He denies syphilis.

Present Illness.—For the past eight weeks the patient has complained of indigestion and palpitation of the heart. Four weeks ago, July 12, he had a severe attack of vomiting, and has had frequent similar attacks since this time. Since the onset of these attacks of vomiting he has been quite breathless on slight exertion, and latterly has noticed that there was some swelling of his legs.

Condition on Admission.—Edema of the legs and scrotum and well-marked signs of compression of the left lung are present. The liver is palpable at the umbilicus. The temperature is 99.8 F. The respirations are from 28 to 32 per minute.

Heart.—The upper limit of cardiac dulness lies at the first interspace, to the right 3¾ inches and to the left 8 inches from the midsternal line. Pulsation over the precordium is very slight. There is a distant soft systolic murmur heard over the region of the apex. The first and second sounds are heard everywhere, but are very distant. There is a pleuropericardial friction-rub heard in the third and fourth left interspaces.

Course of Disease.—Aug. 13, 1911: The fourth left costal cartilage was removed, the pericardium opened and a pint of hemorrhagic fluid withdrawn.

Aug. 18, 1911: For several days the patient has had irregularity of the heart, the result of fibrillation of the auricles. To-day the pulse is regular, the *a* wave has appeared again.

Aug. 25, 1911: The cardiac dulness has been greatly reduced by tapping.

Sept. 14, 1911: The patient was tapped again to-day and 2½ pints of blood-stained fluid were removed.

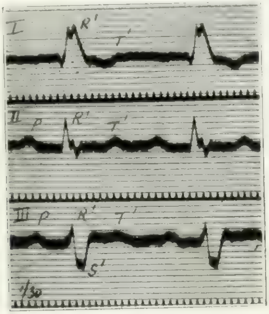

Fig. 1.—Electrocardiograms. Case 4. The *P-R* interval measures 0.2 second. The *Q-R-S* interval is increased, measuring 0.13 second. In Lead I, the initial deflection *R'* is conspicuous as a broad summit with a markedly split apex. The final deflection *T'* is inverted, lying in a direction opposite to the prominent summit *R'*. In Lead II, the initial deflection *R'* appears as a conspicuous peak with marked notching. The final deflection *T'* is upright, lying in the same direction as *R'*. In Lead III, *R'* is present, but *S'* appears as a prominent broad depression with marked notching of the base. The final deflection *T'* is upright, lying in a direction opposite to the prominent deflection *S'*. The increased duration of the opening phases of the complex, the conspicuous notching, and the direction of the final deflection *T'* in relation to prominent deflections *R'* and *S'*, are apparent.

Sept. 26, 1911: A note was made as follows: The pericardium is filling again. The pulse has remained almost continuously regular. On one or two occasions the patient has noticed some palpitation of the heart. The temperature has been normal throughout, except for a few days after the operation.

Sept. 11, 1912: The patient was seen on this date and is apparently in very fair condition. There is very little breathlessness. The limits of cardiac dulness are considerably reduced and no effusion is demonstrable in the pericardium.

Subsequent History.—July, 1913: The patient is alive and apparently in good condition.

Case 5.—*Cardiac hypertrophy, myocarditis, auricular fibrillation, arteriosclerosis, Cheyne-Stokes respiration, cardiac failure and death.* (Electrocardiograms, Fig. 2.)

Patient.—J. P., a hotel-keeper, aged 69, was admitted to the hospital Nov. 11, 1911, complaining of breathlessness, feelings of faintness and swelling of the legs.

Family History.—Negative.

Personal History.—The patient remembers no past illness. He has not had rheumatic fever and denies syphilis. He has drunk beer in moderation, but has been a heavy smoker.

Present Illness.—In October, 1907, the patient met with an accident, which he states injured his spine. He was laid up at this time some weeks, but made a good recovery, though he insists that his heart has been weak since the mishap. In October, 1911, he contracted a severe cold and had a slight pneumonia, being ill in bed for some weeks. From this time his symptoms have increased. At present he complains of great breathlessness on slight exertion, general lassitude and frequent attacks of dizziness. Recently his legs have become swollen and he has noticed puffiness about the eyes.

Condition on Admission.—The patient is well built, but exhibits conspicuous breathlessness. There is a slight degree of cyanosis present. The legs are edematous; the liver is not palpable; the flow of urine is abundant and albumin is excessive. The pulse is very irregular and weak (auricular fibrillation), rate 80 per minute. The arteries show thickening; the systolic blood-pressure is 160 mm. Hg (strongest beats).

Heart.—The heart's impulse is not visible; the limits of dulness are difficult to ascertain as the lungs encroach so much on it. The heart-sounds are faint; the first sound is reduplicated; no murmurs are heard.

Course of Disease.—During the patient's stay in the hospital Cheyne-Stokes breathing was often observed; he became delirious from time to time, and on occasions was in a state of coma. He was treated with digitalis and, though his life was despaired of, he was eventually discharged a good deal improved.

Readmission.—A year later he was again admitted with the same symptoms.

Nov. 1, 1912: The legs are again swollen, he has much cough and breathlessness and sleeps badly. His symptoms have been increasing for the past three weeks and he has lost in weight. The physical signs are much the same as on his first admission.

The heart is still irregular, but of normal rate. The upper limit of cardiac dulness lies at the third interspace, to the right 1½ inches and to the left 5½ inches from the midsternal line. There are no murmurs; the first sound is faint, but not reduplicated. The liver is just palpable.

Course of Disease.—Cheyne-Stokes respiration was observed on many occasions and he was sometimes delirious at night. Although constantly breathless cyanosis was never prominent. He again so far recovered as to be able to leave the hospital much improved.

Readmission (March 3, 1913). (Note T. L.) The patient lies propped up in bed. His lips are pale and very slightly cyanotic. His breathing is labored and from time to time shows periodicity in depth. There is slight edema of the ankles. The pulse-rate is 84 to the minute and irregular (auricular fibrillation and defect of the right bundle branch as before). The signs in the heart remain unaltered. There is impairment of resonance at the bases of both lungs. The liver is easily palpable below the costal margin.

March 5, 1913: The respirations are irregular and show periodicity in depth. No apneic periods, however, are present.

March 19, 1913: There is to-day a good deal of improvement in the patient's breathing; it is easy and almost natural during the day, but tends to show a periodicity at night.

March 21, 1913: The patient was discharged to-day in a much improved condition. There was at this time no breathlessness if he moved slowly, and his color was good. During his stay in the hospital the temperature was normal. The systolic blood-pressure ranged between 130 and 140 mm. Hg. The urine varied in quantity between 1,100 and 2,500 c.c. per diem. The reaction was acid; the specific gravity ranging from 1.010 to 1.012, except just after admission, when it was 1.022; albumin, blood and casts were not found.

Readmission (April 3, 1913).—Seen in the out-patient's department on this day, the patient was evidently much worse and was readmitted to the hospital. He has been voiding very little urine and what is passed is dark in color. He is considerably, but not deeply, cyanosed and is very dyspneic. The breathing is rapid, 32 to the minute, and labored, while he lies well propped up. The liver is again large, and there is impairment of resonance at the bases of both lungs and numerous crepitations are heard over the whole chest. The signs in the cardiovascular system are unaltered.

April 6, 1913: Cheyne-Stokes breathing with long apneic pauses is observed at night. Patient is still cyanotic. Electrocardiograms were taken on this date.

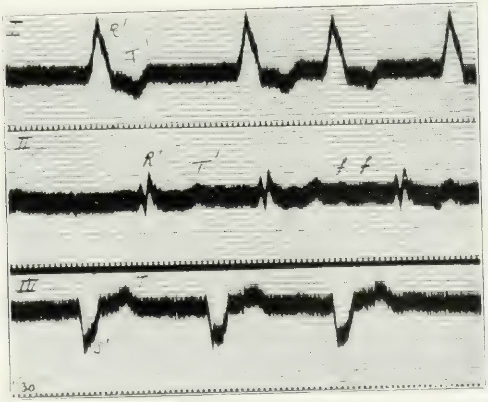

Fig. 2. Electrocardiograms, Case 5. The *P-R* interval could not be determined owing to the constant presence of auricular fibrillation. The *Q-R-S* interval is increased, measuring 0.16 second. In Lead I, the increased amplitude and the marked notching of the initial deflection *R'* are conspicuous. *T'* is inverted lying in a direction opposite to the summit *R'*. In Lead II, *R'* shows marked splitting. *T'* is upright lying in the same direction as the deflection *R'*. In Lead III, the broad, markedly notched deflection *S'*—in a direction opposite to the summit *R'* in Lead I—is conspicuous. *T'* is upright lying in a direction opposite to the initial deflection *S'*. The diphasic character of the ventricular complex is apparent in Leads I and III.

April 7, 1913: The dyspnea is still conspicuous. In the morning 30 ounces of urine were withdrawn by catheter and a little albumin was found. An attempt was made to bleed the patient, but the flow was so poor that it had to be abandoned. A urea estimation gave 2.3 gm. per liter of blood. (Cotton.) Death occurred without further warning the same day, the patient collapsing, becoming very cyanotic and the respirations ceasing after a few forcible inspiratory efforts.

During his last illness the amount of urine varied between 100 and 900 c.c. per diem. It was dark in color, of acid reaction, the specific gravity ranging between 1.020-1.030, and was loaded with urates; once only a faint trace of albumin was found. The systolic blood-pressure varied between 116 and 138 mm. Hg. The temperature was subnormal throughout.

Post-Mortem Examination (April 8, 1913).—Deep cyanosis. Dropsy of the legs. The pleural cavities each contain about one pint of clear fluid. There is an excess of fluid in the pericardial and peritoneal cavities. The lungs are slightly emphysematous; the bases are edematous and congested. The heart is large and covered with fat; the muscle shows yellow striation. The cavities are dilated and the walls seem hypertrophied. The valves are normal. No antemortem clots were found. The aorta and large arteries show generalized arteriosclerosis with calcareous deposits; the aortic arch is dilated. The liver is large, fatty and congested. The splenic pulp is friable and dark in color. The kidneys are congested; the capsules strip off leaving a slightly torn and granular surface; there are a few scars on the surface, but no cysts. The cortex and medullary substance show narrowing. The brain is normal though the membranes over the vertex are edematous; the remaining organs are normal.

Electrocardiographic curves taken on repeated occasions always showed the same mechanism, namely, fibrillation of the auricles and absent conduction in the right branch of the auriculoventricular bundle. The ventricular rate was always slow, ranging from 60 to 90. (See Fig. 2.)

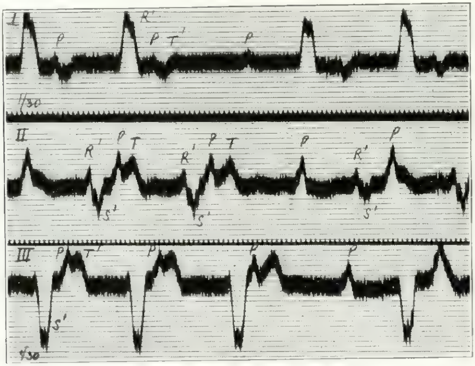

Fig. 3.—Electrocardiograms, Case 6. Note the degree of heart-block present. From time to time a failure of response to the previous auricular contraction is shown. In Lead I, the initial deflection R' appears as a conspicuous summit of increased amplitude and duration, with marked notching. The final deflection T' is inverted, lying in a direction opposite to the prominent R'. The gradual increase in the P-R interval up to the point of the occurrence of the dropped beat is apparent. There is no ventricular response to the second P summit in this lead. In Lead II, R' is present, but the deflection S' appears as a conspicuous depression of increased amplitude and duration with marked notching. The final deflection T' is upright, lying in a direction opposite to the prominent S'. Here again the failure of a ventricular response, following the second auricular contraction, is apparent. In Lead III, R' is absent. The initial deflection S' appears as a depression of greatly increased amplitude and duration, with conspicuous notching. The final deflection T' is upright, lying in a direction opposite to the prominent S'. There is a missed ventricular response after the third P summit.

Case 6.—*Cardiac hypertrophy, mitral disease, paroxysmal tachycardia and auriculoventricular heart-block in varying degrees.* (Electrocardiograms, Fig. 3.)

Patient.—R. S., a bootmaker, aged 64, was admitted to the hospital Dec. 1, 1911, complaining of shortness of breath, attacks of faintness and pain in the chest.

Personal History.—Twelve years ago the patient suffered from a fistula *in ano.* There is no history of any other illness. He denies syphilis. He has been a moderate user of alcohol and tobacco.

Present Illness.—Twelve months ago he first noticed shortness of breath on exertion. For six weeks he has experienced attacks of pain in the chest accompanied by faintness. In some of these attacks he vomits, and on one occasion he lost consciousness. His pulse-rate in the attacks, which were witnessed by his physician, Dr. Alex. Brown of Kentish Town, rose to at least 250 per minute.

Condition on Admission.—The patient is well nourished and shows no sign of breathlessness and little or no cyanosis. The liver is enlarged. There is no dropsy. The temperature is normal. The pulse is regular, its rate being from 72 to 144 per minute; the vessel-wall is thickened. The systolic blood-pressure varies between 64 and 130 mm. Hg.

Heart.—The heart's impulse is neither visible nor palpable. The limits of cardiac dulness lie at the fourth rib above, to the right at the left sternal margin, and to the left in the fifth space four inches from the midsternal line. There is a blowing systolic murmur at the apex; and also a systolic murmur at the aortic cartilage.

Subsequent History.—Unknown.

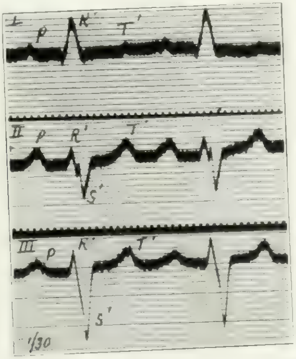

Fig. 4.—Electrocardiograms, Case 7. The *P-R* interval measures 0.21 second. The *Q-R-S* interval measures 0.11 second. In Lead I, the initial deflection *R'* appears as a peak of increased duration and slight increase in amplitude, with conspicuous notching. The final deflection *T'* is upright, lying in the same direction as the initial *R'*. In Lead II, *R'* is present but inconspicuous. The deflection *S'* appears as a depression of increased duration with marked notching. The final deflection *T'* is upright, lying in a direction opposite to *S'*. In Lead III, the initial deflection *R'* is again inconspicuous. The deflection *S'* appears as broad depression of greatly increased amplitude. The final deflection *T'* is upright, lying in a direction opposite to the prominent *S'*. The increase in the *P-R* interval is apparent in all three leads.

Electrocardiograms.—This case is of especial interest because of the presence of varying degrees of auriculoventricular heart-block, which were present at different times; the patient having been under observation over a long period before his entrance into the hospital. (Fig. 3.) Jan. 17, 1911, the *P-R* interval measured 0.34 second, and Aug. 7, 1912, 0.3 second. Nov. 3, 1912, complete auriculoventricular heart-block was present. Nov. 13, 1911, dropped beats, Feb. 6, 1913, dropped beats, and again Feb. 24, 1913, complete auriculoventricular heart-block was present.

CASE 7.—*Arteriosclerosis, cardiac hypertrophy, aortic disease, myocarditis, cardiac failure and death.* (Electrocardiograms, Fig. 4.)

Patient.—W. S., a coal-porter, aged 52, was admitted to the hospital Feb. 24, 1912, complaining of abdominal pain, shortness of breath and sleeplessness.

Family History.—Negative.

Personal History.—The patient gives no history of any past illness. Syphilis and rheumatic fever are both denied. For many years he has drunk six pints of beer daily and has used four ounces of tobacco a week. His work has been heavy.

Present Illness.—The patient states that his present illness began about a month ago (Jan. 24, 1912). At this time he first noticed shortness of breath on any slight exertion. This was soon followed by dull aching pains referred to the upper abdomen, and by sleeplessness. The shortness of breath has gradually increased, a troublesome cough has developed and latterly he has complained of feeling sick on rising in the morning.

Condition on Admission.—The patient is pale and orthopneic. There is no cyanosis. The teeth are carious. The temperature is normal. There is neither dropsy nor ascites. The respirations are 36 to the minute. The urine is normal. The pulse is regular, 90 to the minute, of the water-hammer type. Capillary pulsation is present. Pulsation of the carotids is visible to the lobes of the ear. The arteries are thickened. The systolic blood-pressure is 110-140 mm. Hg. The liver is palpable an inch below the costal margin.

Heart.—The point of maximum impulse is in the fifth and sixth interspaces five inches from the midsternal line. The upper limit of cardiac dulness lies at the third rib; to the right one inch and to the left five inches from the midsternal line. At the apex and over the aortic area systolic and early diastolic murmurs are heard; the first sound is inaudible.

Subsequent History.—During a month's stay in the hospital his acute symptoms, with the exception of slight breathlessness on exertion, entirely subsided. The respirations fell to 20 per minute when at rest. Otherwise his condition remains unchanged. He left the hospital but died some time afterward; no necropsy was obtainable.

CASE 8.—*Cardiac hypertrophy, myocarditis, mitral disease and pericarditis.*

Patient.—H. C., a domestic, aged 18, was seen March 16, 1912, complaining of shortness of breath and some pain in the chest, in front. A note made at this time states that the patient had pneumonia at the age of 5; she is also said to have had swelling of the knees and ankles on several occasions, which suggest a rheumatic history. There has been at different times some edema of the legs. Infantilism is conspicuous.

Heart.—The limit of cardiac dulness lies 3½ inches to the right and 6 inches to the left of the midsternal line. There is an early diastolic and systolic thrill at the apex. The first sound at the apex is reduplicated, associated with early diastolic murmurs. A friction-sound is heard over the base of the heart. The aortic and pulmonary sounds are normal.

Subsequent History (June 14, 1913).—The patient is alive, but her condition is much as noted above.

Electrocardiograms.—The *P-R* interval measures 0.29 second. In Lead I, *S′* and *T′* deflections are seen, the whole curve being diphasic and the initial phase (*S′*) long. In Lead II the curve is similar, but a small spike *R′* is added. In Lead III, *R′* opens the complex and is followed by a *T′* deflection; a small *S′* is also present.

CASE 9.—*Myocarditis, aortic regurgitation, cardiac failure and death.*

Patient (Electrocardiograms, Fig. 5).—S. R., a gas-fitter, aged 36, was admitted to the hospital April 9, 1912, complaining of shortness of breath, cough, swelling of the feet and sleeplessness.

Personal History.—There is no history of any past illness. The patient has seen service in South Africa.

Present Illness.—The onset of his present illness is attributed by the patient to an attack of sore throat and bronchitis, which he had four months ago (January, 1912). He was examined at this time and his heart was found to be affected. Recently the shortness of breath has increased to such an extent that he cannot take the slightest exercise and work is impossible.

Condition on Admission.—The patient is pale but well nourished. There is slight cyanosis. The respirations are hurried, 28 to the minute, a little labored. Some venous engorgement and signs of pulmonary congestion are present. There is edema of the feet and back. The specific gravity of the urine is 1.023, reaction acid; no albumin is present. The liver is palpable three finger-breadths below the costal margin. The pulse is regular, 106 to the minute, of the water-hammer type. Capillary pulsation is present, though slight. The arteries are tortuous.

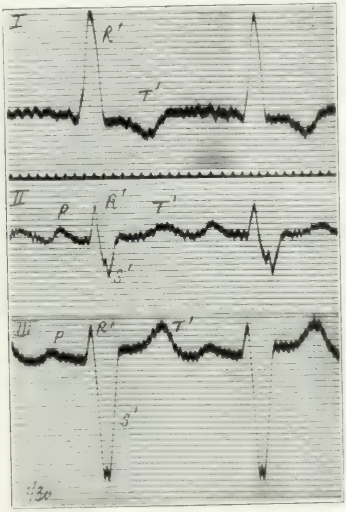

Fig. 5.—Electrocardiograms, Case 9. The *P-R* interval measures 0.17-0.18 second. The *Q-R-S* interval measures 0.1 second to 0.11 second. In Lead I, the initial deflection *R'* is conspicuous as a tall broad summit with slight notching. *T'* is inverted lying in the opposite direction to the summit *R'*. In Lead II, the initial deflections *R'* and *S'* are equally conspicuous. *S'*, however, shows marked notching. *T'* is upright in a direction opposite to the deflection *S'*. In Lead III, the deflection *R'* is present as a short summit, while the depression *S'* is conspicuous as a deep broad deflection with split base. *T'* is upright in a direction opposite to the prominent deflection *S'*. The greatly increased amplitude, the longer duration and the notching of the initial deflections *R'* and *S'* are conspicuous in all leads.

Heart.—The shock of the heart is diffuse and extends well outside the nipple line. The limit of cardiac dulness lies 2 inches to the right and 6¼ inches to the left of the midsternal line. At the apex a systolic and a faint diastolic murmur are heard; over the aortic area to-and-fro murmurs are heard, maximal in intensity at this point; over the pulmonary area the same murmurs, though fainter, are audible. The second sounds are not heard.

Course.—After a month's stay in the hospital the patient's condition improved considerably, and he was discharged at his own request. A few weeks later he was admitted to an infirmary, with an exacerbation of all his symptoms and with aggravated dropsy. He died within a few hours. No necropsy was obtained.

Case 10.—*Rheumatic carditis, aortic disease, angina pectoris, high blood-pressure, alternation, cardiac failure and death.* (Electrocardiograms, Fig. 6.)

Patient.—R. B., aged 45, came under observation June 6, 1912, complaining of pains in the chest and breathlessness.

Family History.—The patient's father and an uncle died suddenly of "heart disease." A sister has had rheumatic fever. The patient's child, aged 9, was examined and found to have mitral stenosis.

Personal History.—The patient has suffered from rheumatic fever on five occasions, the first attack being at the age of 12 and the last at 30. He became almost deaf at 40. At 43 he had an attack of pleurisy. Syphilis is denied.

Present Illness.—The present illness really began twenty-eight years ago, when the patient was treated at a London hospital for angina pectoris. The pains have been severe of late and radiate over a wide area; they are accompanied by feelings of giddiness, suffocation and anxiety, and are brought on by the slightest exertion. Lately his legs have become swollen and breathlessness has developed.

Condition on Admission.—The patient is pale and poorly nourished. There is a little dropsy of the extremities. Cyanosis and dyspnea are absent. The carotids pulsate vigorously and the veins of the neck are abnormally prominent. The liver is not enlarged. The urine contains no albumin. The pulse is of the water-hammer type and occasionally intermits. Capillary pulsation is present. The alteries are thickened. The systolic blood-pressure lies between 180 and 200 mm. Hg.

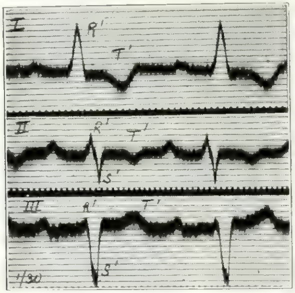

Fig. 6.—Electrocardiograms, Case 10. The *P-R* interval measures 0.21 to 0.23 second. In Lead I the initial deflection R' appears as a slightly broadened peak with notching of the side and apex. T' is inverted lying in the opposite direction to the summit R' In Lead II, the initial deflection R' is conspicuously notched. The deflection S' is plainly seen. T' it will be noted is again inverted, lying in a direction opposite to R'. In Lead III, the greatly increased amplitude of the initial deflection S' is apparent. S' shows marked splitting of its base. R' is inconspicuous. T' is upright lying in a direction opposite to the prominent initial deflection S'. The increase in the *P-R* interval is apparent in all leads

Heart.—The visible impulse is diffuse. The upper limit of cardiac dulness is at the second rib; the limit of dulness to the right is 1½ inches and to the left 7½ inches from the midsternal line. At the apex the first sound is replaced by a systolic bruit, followed by an early diastolic murmur. At the aortic cartilage a diastolic thrill and murmur are detected; the second sound is absent.

Course.—The patient was under observation for over twelve months, during which period the physical signs and symptoms remained unaltered. With rest the pain disappeared, only to reappear as soon as the patient was about again.

He died suddenly in August, 1912. No post-mortem examination could be obtained.

Electrocardiograms.—The electrocardiographic curves were constantly of the same type, being those associated with deficient conduction of the right branch of the auriculoventricular bundle. In this case extraventricular systoles were recorded appearing in a direction opposite to the prominent initial deflections in all leads, hence the premature beat arose in the opposite ventricle from the aberrant beat, that is, from the right and basal portion of the heart.

CASE 11.—*Arteriosclerosis, myocarditis, aortic disease, cardiac failure and death.* (Electrocardiograms. Fig. 7).

Patient.—C. H., a seaman, aged 47, was admitted to the hospital July 20, 1912, complaining of shortness of breath and swelling of the legs.

Family History.—A brother is said to have had rheumatic fever: otherwise the family history is negative.

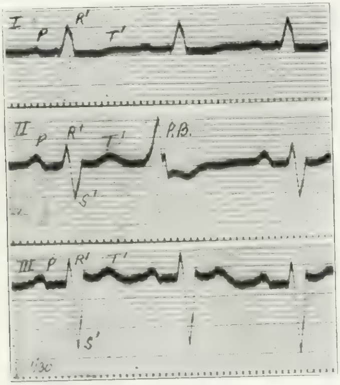

Fig. 7.—Electrocardiograms, Case 11. The P-R interval measures 0.2 second. In Lead I the initial deflection R' appears as a somewhat broadened summit with marked notching. T' is upright in the same direction. In Lead II, the initial deflection R' is plain. The deflection S' shows an increase in amplitude and conspicuous notching. T' is upright lying in a direction opposite to the prominent S'. The single premature beat recorded in the figure—P-B.—coincides with the auricular summit P, which does not appear. The premature beat lies in a direction opposite to the prominent aberrant deflection S'. In Lead III, the initial deflection R' is present. The deflection S' appears as a conspicuous depression of greatly increased amplitude, with slight notching. T' is upright in a direction opposite to the prominent deflection S'. The premature beats recorded in this lead (none is shown in the figure), were in the same direction as the aberrant curve.

Personal History.—There is no history of any illness, with the single exception of an attack of "bronchitis," which the patient had eighteen months ago. He has never had rheumatic fever. He denies syphilis.

Present Illness.—The patient attributes the onset of his present illness to the "bronchitis" which he had eighteen months ago. This attack was soon followed by shortness of breath, which has increased steadily. During the past weeks his legs and abdomen have become swollen.

Condition on Admission.—The patient is florid. The conjunctivae are tinged with bile. He is cyanotic and very orthopneic. There are signs of fluid in the right chest. There is marked edema of the back, legs and scrotum, and abdominal ascites is present. The liver is palpable below the umbilicus and pulsating. The respirations are 32 to the minute. The temperature is normal. The specific gravity of the urine 1.012; the normal amount is reduced and albumin is present in excess. The pulse-rate is from 118 to 120 per minute, occasionally intermittent, of the water-hammer type. Capillary pulsation is present. The arteries are thickened. The systolic blood-pressure is low, from 98 to 102 mm. Hg.

Heart.—The point of maximum impulse is neither visible nor palpable. The upper limit of cardiac dulness lies at the fourth interspace, to the right at the right sternal margin and to the left 4½ inches from the midsternal line. There is an apical systolic murmur and a faint first sound. At the aortic area systolic and diastolic murmurs are heard.

Course.—The patient was given infusion of digitalis (2 drams three times daily), but showed no improvement. He died July 27, a week after admission. Necropsy was refused.

Electrocardiograms—In three observations, extending over a period of six weeks, the *P-R* interval measured 0.26, 0.16 and 0.2 second, the last two days before death. The curves were always of the same type, being those seen in association with defective conduction of the right branch of the auriculoventricular bundle. The extra systoles recorded were in a direction opposite to the prominent initial deflection *S′*, of the aberrant curve, in Lead II, but in the same direction as the aberrant curve in Lead III (Fig. 7).

CASE 12.—*Myocarditis and aortic disease. Febrile auriculoventricular heart-block of varying degree.* (Electrocardiograms, Figs. 8 and 9.)

Patient.—W. C., a bookbinder, aged 32, was admitted to the hospital Aug. 16, 1912, complaining of shortness of breath and pains in the chest.

Personal History.—The patient states that he always felt perfectly well until about six years ago. He has never had rheumatic fever. He denies syphilis. He is a heavy smoker, but uses alcohol in moderation.

Present Illness.—The patient dates the onset of his present illness back about six years, when he first began to notice shortness of breath after any unusual exertion. This shortness of breath has increased, and for some months now he has had pain of an aching character over the precordial area. He is unable to lie on the right side at night.

Condition on Admission.—The patient, thin and pale, lies propped up in bed and quite breathless. There is no dropsy or liver enlargement. The urine contains no albumin. The pulse is regular, of the water-hammer type, ranging from 64 to 88 per minute. The arteries are thickened. The systolic blood-pressure varies from 110 to 148 mm. Hg. The temperature is 99 F.

Heart.—The heart's impulse is diffuse in the fourth, fifth and sixth interspaces. The limits of cardiac dulness lie at the third rib above, ¾ of an inch to the right and 5½ inches to the left of the midsternal line. At the apex a short, sharp first sound and a low-pitched presystolic murmur are heard. The second sound is faint and is followed by an early diastolic murmur. At the base a systolic thrill is felt, and rough to-and-fro murmurs are audible, having their maximum intensity at the aortic cartilage. The second sound is not heard.

Course.—The temperature rose to 100.5 F. the day after admission, but fell gradually to normal by August 22. After several weeks rest, his symptoms being considerably improved, he was discharged.

Readmission (May 27, 1913). The patient complains of throbbing pain in the chest, which has increased during the past three weeks.

Condition on Readmission.—There is no cyanosis or dyspnea. The pulse is regular in force and rhythm, of water-hammer type. Capillary pulsation present. The arteries are sclerosed, as noted formerly.

Heart.—The cardiac dulness lies at the third rib above, to the right at the right sternal margin, to the left 5½ inches from the midsternal line. There

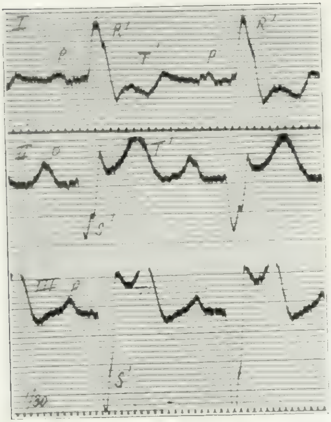

Fig. 8.—Electrocardiograms. Case 12. The *P-R* interval measures 0.18 second. The *Q-R-S* interval measures 0.13 second. In Lead I the initial deflection *R′* appears as a broad, tall peak with conspicuous notching. *T′* is inverted lying in a direction opposite to the prominent deflection *R′*. In Lead II *R′* is wanting, the initial deflection *S′* appears as a deep depression of increased duration as well as amplitude, with conspicuous notching. *T′* is exaggerated, upright, in a direction opposite to the prominent deflection *S′*. In Lead III *S′* is conspicuous as a deflection of greatly increased amplitude with marked notching. *T′* is upright in a direction opposite to that of the conspicuous deflection *S′*. The increase in the *P-R* interval and the great increase in the duration and amplitude of the initial phases of the ventricular complex is apparent in all three leads. The bizarre character of the curves recorded on this date is in striking contrast to the curves taken on the following day.

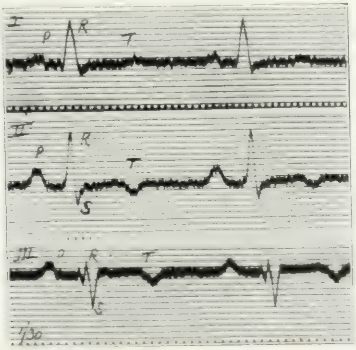

Fig. 9.—Electrocardiograms. Case 12. The *P-R* interval measures 0.18 second. The *Q-R-S* interval measures less than 0.1 second. In Lead I, *R* is present as a peak of short duration and amplitude. *T* is upright, lying in the same direction as the peak *R*. In Lead II, *R* and *S* are present. R appearing as a deflection of short duration. *T* is inverted lying in a direction opposite to the peak *R*. In Lead III the initial deflections *R* and *S* are not exaggerated. *T* is again inverted.

is a systolic as well as a presystolic murmur at the apex, the latter is heard only with every fifth or sixth beat. Over the aortic area there is a double murmur. The specific gravity of the urine is 1.028; a trace of albumin is present.

June 12, 1913: Under rest the patient's condition, so far as subjective symptoms are concerned, has materially improved. His pain has been relieved and he feels much more comfortable. The physical signs remain unchanged.

Electrocardiograms.—This case is of especial interest, in that during the period the patient has been under observation, varying degrees of heart-block have been noted.

A comparison of the electrocardiographic curves taken on the second and third day after his first admission (August, 1912) is most interesting and instructive; the exaggerated, bizarre form recorded August 18 (Fig. 8), the result of defective conduction of the right branch of the auriculoventricular bundle, due to his febrile attack, giving place to the very different curve recorded on the next day (Aug. 19, 1912). On this date the ventricular portions of the curves have entirely altered (Fig. 9). There is no evidence of any defect in conductivity of the right branch of the bundle, but only of a relative preponderance of the left ventricle.

These two figures are most instructive, illustrating as they do the occurrence of a temporary defect in conductivity of the right branch of the auriculoventricular bundle (Fig. 8), and on the subsidence of this acute defect, the physiological electrocardiograms for this patient (Fig. 9) indicative only of a relative left-ventricular hypertrophy. In addition to the very apparent differences in the duration and amplitude of the opening phases, as well as in the direction of the prominent deflections in the various leads of the two figures, a comparison of the direction of the summits T' and T in the corresponding leads is most important. In each of the corresponding leads, of the two figures, it will be noted that where T' points in one direction T points in the other, and that, throughout, T is much less conspicuous than T'.

In Figure 8, T', in accordance with the general rule in these cases, lies in a direction opposite to that of the prominent initial deflections in all leads. In Figure 9 the inversion of T in Lead II is in itself of pathological significance.

Note the absence of notching in the ventricular complex of Figure 9.

These two figures may well serve to emphasize the differences between the curves obtained as a result of a defect in conductivity of the right branch of the auriculoventricular bundle, and those due to a relative hypertrophy of the left ventricle.

CASE 13.—*Rheumatic myocarditis, pleurisy with effusion, displacement of the heart and cardiac failure.* (Electrocardiograms, Fig. 10.)

Patient.—R. A., aged 35, was admitted to the hospital Sept. 11, 1912, complaining of shortness of breath and swelling of the legs.

Family History.—Negative.

Personal History.—At the age of 18 the patient was ill for three months with acute rheumatic fever. Subsequently he had many similar, though less severe attacks, until he was 28. Five months ago he had an acute pleurisy with effusion; was tapped and a large amount of fluid was withdrawn from the left pleura. He has used alcohol in moderation and does not use tobacco.

Present Illness.—During the past seven years the patient has been quite free from any symptoms of acute rheumatic fever, but states that for the past seven months he has suffered from a feeling of exhaustion after slight exertion, and from very marked shortness of breath since his pleurisy five months ago. He further states that, to his knowledge, his heart has been affected for ten years at least.

Condition on Admission.—The patient is thin and poorly developed. He has a bad pyorrhea. He is slightly cyanotic, and dyspnea is marked. On the left side the movements of the chest are limited and tubular breathing is heard at the apex behind. There is dulness at the base of the left lung and the breath-sounds are weak. Friction-sounds are heard in the axillary region. There is slight edema of both legs. The temperature is normal. The pulse is regular, from 76 to 104 per minute: the arteries are a little thickened; the systolic blood-pressure varies from 98 to 134 mm. Hg.

Heart.—The point of maximum impulse lies in the fourth interspace, 2 inches inside the right nipple-line. There is a diffuse pulsation over the right side of the chest internal to the main impulse. The limits of cardiac dulness lie at the third rib above, and 2½ inches to the right and left of the midsternal line. The first sound is inaudible at the apex, the second sound is accentuated and a coarse systolic murmur is heard. The second sound is reduplicated at both pulmonary and aortic cartilages. A pleuropericardial friction-rub is heard over the left half of the precordium. Roentgenoscopy showed great displacement of the heart to the right, with enlargement, but no trace of fluid could be seen.

Subsequent History.—After a sufficient period of rest in the hospital the patient so far improved as to be able to leave. So far as is known at present (June 14, 1913) he is still living.

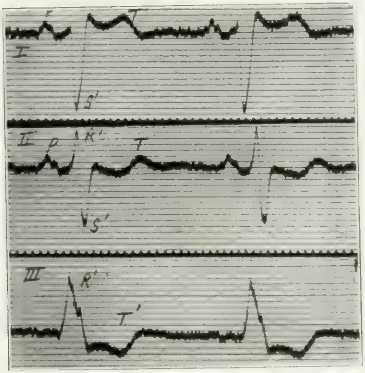

Fig. 10.—Electrocardiograms. Case 13. The *P-R* interval measures 0.13 second. The *Q-R-S* interval measures 0.13 second. In Lead I, *R'* is absent, the initial deflection *S'* appearing as a depression of greatly increased amplitude (apex negativity) with suggestive notching at the extreme base. The summit *T'* is upright, lying in a direction opposite to the prominent deflection *S'*. In Lead II, *R'* is present but the deflection *S'* is of greater amplitude and duration, again with suggestive notching of the base. *T'* is upright in a direction opposite to the prominent deflection *S'*. In Lead III, the initial deflection *R'* is present as a conspicuous summit of increased duration and amplitude, with marked notching. *T'* is again conspicuous, inverted, lying in a direction opposite to the prominent initial deflection *R'*. When compared with all the other accompanying figures, it will be seen that the direction of the prominent initial deflections in Leads I and III are in the opposite directions. It has been shown that in lesions involving the left branch of the auriculoventricular bundle the initial deflection in Lead I is always downward (apex negative) while in Lead III, it is always upward (base negative).

This case is of especial interest in that it is the single instance, in the series, of involvement of the left branch of the auriculoventricular bundle.

Case 14.—*Arteriosclerosis, cardiac hypertrophy, myocarditis, alternation, cardiac failure and death.*

Patient.—W. P., a waterside laborer, aged 62, was admitted to the hospital Nov. 1, 1912, complaining of faintness and shortness of breath.

Personal History.—With the exception of an attack of pleurisy twelve years ago, there is no history of any acute illness. The patient has had repeated attacks of tonsillitis to which he has paid little attention. He also states that he has suffered from so-called "muscular rheumatism" for many years, but that he had not had acute rheumatic fever. A sister is said to have had a history of vague "rheumatic" pains. He denies syphilis. He has used but little alcohol and smokes in moderation.

Present Illness.—For the past eighteen years the patient has felt less fit for work than previously, and from time to time has experienced shortness of breath. Eight years ago while carrying heavy wheat-sacks he had an attack of faintness and was forced to stop work. He noticed at this time that his scrotum was a little swollen and that it increased in size during the next two days. He was treated at a hospital, improved and went back to work. A year later he had a similar attack and was again incapacitated. He has not been well since this attack in 1906, and has been treated at several institutions recently for an aggravation of the same symptoms and faintness.

Condition on Admission.—The patient is pale and spare. The conjunctivae are bile stained; there is a little cyanosis of the mucous membranes. He has hurried and irregular breathing. Dropsy of the legs, genitalia and scrotal region is present. The urine is acid, specific gravity 1.018, and a trace of albumin is present. The liver is enlarged and there is some ascites. There is dulness at the left base of the chest with weak breath-sounds; faint râles are heard at both bases. The temperature is normal.

Heart.—The heart's dulness extends 2 inches to the right and 6½ inches to the left of the midsternal line. There are no murmurs. The heart-beats are either regular at 80 or 90 per minute, when cantering rhythm is heard; or the beats are in couples, when three sounds accompany each beat of the couple. When the coupled beats are present the pulse-rate is halved. The arteries are thickened; the systolic blood-pressure is 120 mm. Hg. Venous pulsation in the veins is conspicuous and these vessels are enlarged.

Course.—After a prolonged stay in the hospital, the dropsy and many of the signs of engorgement were relieved, and the breathing was much freer. The patient died Feb. 13, 1913, shortly after leaving the hospital.

Electrocardiograms.—The P-R interval could not be determined owing to the presence of auricular fibrillation. The ventricular complexes were similar to those shown in Figure 3. The premature beats recorded were in all leads — I, II and III — in a direction opposite to the aberrant beat, and hence arose from the right and basal portion of the ventricle.

CASE 15.—*Myocarditis in gouty subject, anginal symptoms, syncopal attacks, extrasystoles and alteration.* (Electrocardiograms, Fig. 11).

Patient.—J. W., a man, aged 68, was first seen Nov. 6, 1912, complaining of attacks of faintness and occasional loss of consciousness.

Personal History.—For many years the patient has been subject to acute attacks of gout. For a few years he has had occasional attacks of faintness and throbbing in the chest and a feeling of great distress; these symptoms coming on always after exertion. In some of the attacks he has lost consciousness for a few seconds. These attacks have not been frequent, and as a rule have been isolated, but on one occasion five attacks occurred one after another. The feeling of distress is relieved by nitroglycerin.

Condition on Admission.—The patient is heavily built and shows little or no dyspnea or cyanosis. The urine contains no albumin and there are no signs of dropsy. The pulse intermits occasionally, the rate is 78 to the minute. The systolic blood-presure is 160 mm. Hg.

Heart.—The impulse is diffuse, there is an extension of dulness towards the left side. No murmurs are heard, but the first sound is reduplicated at the apex and base.

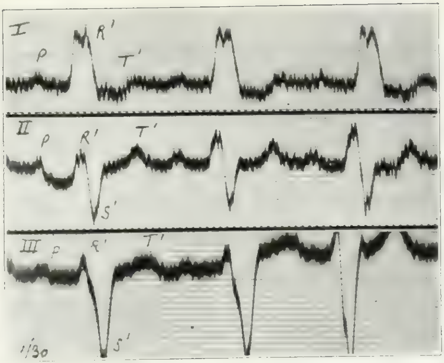

Fig. 11.—Electrocardiograms, Case 15. The *P-R* interval measures 0.2 second. The *Q-R-S* interval measures 0.16 second. In Lead I, the initial deflection R' appears as a broad wide summit, with conspicuously split top. The final deflection T' is inverted lying in a direction opposite to the deflection R'. In Lead II, R' is present as a short summit with marked notching, the deflection S' is conspicuous as a deep depression with notching, the final deflection T' is upright lying in a direction opposite to the prominent deflection S'. In Lead III, R' is inconspicuous, S' appears as a deep depression of exaggerated amplitude and duration, with marked notching. The final deflection T' is again upright, lying in a direction opposite to the prominent deflection S'. The increase of the *P-R* interval and the increase in the duration and amplitude of the early phases of the complex is apparent in all leads. The single premature beat recorded in Lead III is in the same direction as the prominent deflection S'.

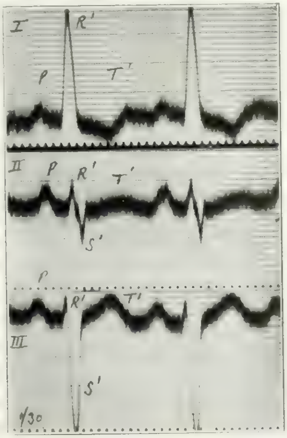

Fig. 12.—Electrocardiograms, Case 16. The *P-R* interval measures 0.14 second. The *Q-R-S* interval is not increased, measuring 0.08 second. In Lead I, the initial deflection R' is conspicuous as a tall peak of greatly increased amplitude. The final deflection T' is inverted lying in a direction opposite to the prominent summit R'. There is no notching. In Lead II, the initial deflection R' is present and equally as conspicuous as the deflection S'. The final deflection T' is upright. In Lead III, the initial deflection R' is inconspicuous, the deflection S' appearing as a deep depression of greatly increased amplitude. The final deflection T' is upright in a direction opposite to the conspicuous deflection S'. The increased amplitude of the initial deflections in Leads I and III is apparent, as is the direction of the final deflection T' in relation to R' and S'.

Graphic Records.—The intermissions are the result of premature contractions arising in the ventricle. They are either isolated or occur in short groups. The premature beats are followed by alternation of the pulse.

CASE 16.—*Myocarditis, alternation, Cheyne-Stokes breathing, high blood-pressure and cardiac failure.* (Electrocardiograms, Fig. 12.)

Patient.—D. E., a physician, aged 54, was seen Nov. 16, 1912, complaining of breathlessness on exertion.

Personal History.—The patient had an attack of erysipelas when 15. Otherwise, with the single exception of an attack of pleurisy some years ago, his history is negative. He has been moderate in his use of alcohol, but has always eaten very heartily. His life has been very active.

Present Illness.—For three months past he has suffered from breathlessness, which has been increasing steadily. At present it is brought on by even slight exertion. There has been no pain, soreness of the chest or palpitation.

Condition on Admission.—The patient is heavily built, florid and a little cyanosed. He is of a nervous temperament. There is slight dropsy of the legs, but no enlargement of the liver. He has a tendency to Cheyne-Stokes breathing. The urine contains no albumin.

Heart.—The apex-beat cannot be found. The area of the heart's dulness is increased to the right and left. At the apex, gallop rhythm is heard. There are no murmurs. At the base the sounds are normal. The pulse intermits occasionally; the arteries are much thickened; the systolic blood-pressure is 210 mm. Hg.

Subsequent History.—The patient went home and died in August, 1913,

CASE 17.—*Rheumatic myocarditis, cardiac hypertrophy, aortic disease, ventricular extrasystoles and cardiac failure.* (Electrocardiograms, Fig. 13.)

Patient.—W. O., a hotel porter, aged 27, was admitted to the hospital Feb. 4, 1913, complaining of pain in the chest, ankles and knees.

Family History.—Negative.

Personal History.—The patient had chorea at 11, and rheumatic fever at 17. Following the rheumatic fever, ten years ago, his heart was affected, and he has had shortness of breath ever since.

Present Illness.—The patient refers the commencement of his present acute symptoms to the sudden onset, about ten days ago (January 26), of a sharp and severe pain in the chest, in the region of the heart, which is aggravated by breathing or by coughing. Three days later his ankles became swollen, red and tender, and subsequently his knees also. The patient has been short of breath for the past ten years, but this has been much worse during the past week.

Condition on Admission.—The patient's temperature is 101 F. Both knees and ankles are swollen, but not red or tender; he is sweating profusely. The pulse is typically water-hammer in character, showing occasional extrasystoles. Capillary pulsation is plainly visible. There is a marked pulsation of the vessels in the neck. The arteries are not thickend. No rheumatic nodules are present.

Heart.—There is pronounced heaving of the entire left side of the chest, and a distinct shock palpable in the epigastrium. The upper limit of cardiac dulness lies at the third rib, to the right 1½ inches and to the left 6½ inches from the midsternal line. The apex is well outside the left nipple line in the fifth interspace. The first and second sounds are reduplicated; the first over a wide area, heard 3 inches to the right in the fifth interspace. Over the apex there is a systolic murmur. Over the aortic area there is a systolic and a diastolic murmur, the latter being conducted over the entire heart. On admission there were signs of pleurisy with effusion at both bases, and a general bronchitis. The liver was palpable 1½ inches below the costal margin, no pulsation was present.

Course.—By February 14 the temperature had fallen to normal, the swelling of the joints had subsided, the signs of effusion in the chest had wholly disappeared, and the dyspnea was greatly relieved. He was later discharged from the hospital.

Subsequent History (June 18, 1913.)—The patient is alive and in fair condition.

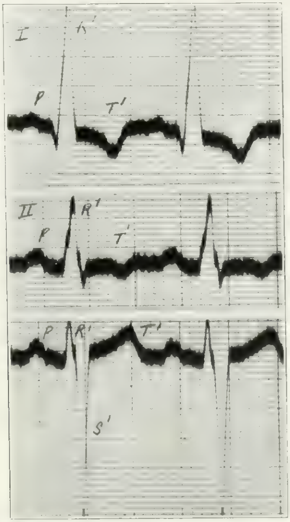

Fig. 13.—Electrocardiograms, Case 17. The *P-R* interval measures 0.17 second. The *Q-R-S* interval measures 0.08 second In Lead I, the initial deflection *R'* is conspicuous as a tall peak of greatly increased amplitude. The final deflection *T'* is inverted, lying in the opposite direction. In Lead II, the initial deflection *R'* is conspicuous as a summit of exaggerated amplitude with marked notching. *S'* is inconspicuous. The final deflection *T'* is again inverted, lying in a direction opposite to the prominent deflection *R'*. In Lead III, the deflection *R'* is present as a short notched peak. The deflection *S'* is conspicuous as a depression of enormously exaggerated amplitude. The final deflection *T'* is upright in a direction opposite to the conspicuous deflection *S'*. The greatly increased amplitude of the initial deflections is apparent at a glance, as is the direction of the conspicuous final deflection *T'* in relation to the prominent deflections *R'* and *S'*.

This case is of especial interest in view of the varying degrees of heart-block noted, the *P-R* interval varying between 0.28 and 0.17 second in curves taken on different occasions.

CASE 18.—*Arteriosclerosis, cardiac hypertrophy, aortic disease, acute pleurisy, cardiac failure and death.* (Electrocardiograms, Fig. 14.)

Patient.—G. C., a milk-carrier, aged 47, was admitted to the hospital Feb. 7, 1913, complaining of shortness of breath, sleeplessness and pain in the chest.

Family History.—Negative. No history of rheumatic fever in the family.

Personal History.—There is a history of syphilis twenty-four years ago, at the age of 23, and of a severe attack of typhoid fever twelve years ago. There is no history of rheumatic fever or of any other illness. The patient has used alcohol and tobacco in moderation.

Present Illness.—About 18 months ago (August, 1911), the patient first began to experience attacks of pain, stabbing in character, starting in the front of the chest over the lower end of the sternum and passing through to the back between the shoulder blades. These attacks came on chiefly at night, and lasted from half an hour to two hours. The pain was often worse just under the left shoulder blade, and the cessation of the pain was frequently followed by paroxysms of breathlessness. A week after the onset of these symptoms he noticed that his feet began to swell, and a few days later he was obliged to give up work. During the past six weeks he has had frequent attacks of distressing shortness of breath associated with this pain in the chest, coming on even though lying quietly in bed; he has also had a troublesome cough unaccompanied with any expectoration.

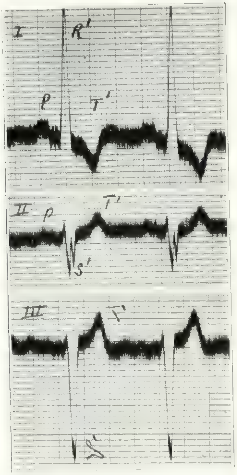

Fig. 14.—Electrocardiograms, Case 18. The *P-R* interval measures 0.2 second. In Lead I, the initial deflection *R'* is conspicuous as a tall peak of greatly increased amplitude. The final deflection *T'* is conspicuous and inverted, lying in a direction opposite to the prominent summit *R'*. In Lead II, the deflection *R'* is absent, the initial deflection *S'* is conspicuous as a markedly split depression. The final deflection *T'* is upright lying in a direction opposite to the prominent deflection *S'*. In Lead III, the initial deflection *S'* is conspicuous as a deep depression of greatly increased amplitude. The final deflection *T'* is upright, lying in a direction opposite to the prominent deflection *S'*. The diphasic character of the complex in Leads I and III, the greatly increased amplitude of the initial deflections, and the direction of the conspicuous final deflection *T'*, in relation to the prominent initial deflections, are apparent.

Condition on Admission.—The patient, a well-developed man, is lying propped up in bed, quite dyspneic. The mucous membranes are pale. There is marked pulsation of the vessels in the neck. The pulse is full and regular in force and rhythm, not compressible, typically water-hammer in character when the arm is raised. The vessel-wall is thickened.

Heart.—The cardiac impulse is visible in the fifth, sixth and seventh interspaces. In the fifth interspace in the anterior axillary line it is heaving. There is a systolic retraction 1 inch below the left nipple. The upper limit of cardiac dulness lies at the third interspace, to the right 1¾ inches and to the left 6½ inches from the midsternal line. At the apex a soft double murmur can be heard over a wide area. Both of these murmurs can be followed up the left border of the sternum. At the aortic cartilage the first sound is obscured by a harsh systolic murmur transmitted upward into the vessels of the neck. The second sound is distant and followed by an early diastolic murmur transmitted downward. The first sound is not heard anywhere.

Respiratory System.—Normal but for a few fine crepitations at both bases posteriorly.

Liver.—The liver is palpable a hand's breath below the costal margin. The spleen is not palpable. There is marked edema of both legs. The specific gravity of the urine is 1.006; a trace of albumin is present but no sugar. No casts seen.

During subsequent observation up to the time of death, April 10, the patient's general condition varied but little from day to day. By February 25 the edema of the legs had disappeared, only to return again later. The pain in the chest was persistent, coming on in paroxysms which left him very dyspneic and greatly depressed.

The cardiac signs remained practically unchanged, though by March 19 the diastolic murmur at the base had wholly obscured the second sound.

About April 1, the pain in the chest became more pronounced, the attacks came on more often and persisted longer. April 5 the patient complained of great pain in the lower right side, and a friction-rub was discovered, heard over the four lower interspaces on the right side behind. April 6 there was well-marked dulness over this area, associated with weak respiratory sounds and decreased vocal resonance and fremitus. On this day a small amount of bright red blood was coughed up. This condition persisted and April 8 a friction-rub was audible over the fifth interspace on the left side anteriorly. On the morning of April 10 a well-marked pericardial friction-rub was heard. There was dulness below the angle of the right scapula, over which area the breath-sounds were weak and the resonance increased. The patient died suddenly during the morning. The temperature just before death was 98 F., and at no time since admission had it been above 99 F.

The systolic blood-pressure was 190 mm. Hg on admission, and had ranged between this figure and 140 mm. Hg, the mean systolic pressure being about 140 mm. Hg. The specific gravity of the urine ranged from 1.006 to 1.028. A trace of albumin was constantly present. No casts were seen.

CASE 19.—*Arteriosclerosis, high blood-pressure, cardiac hypertrophy, myocarditis, mitral disease, nephritis and cardiac failure.* (Electrocardiograms, Fig. 15.)

Patient.—W. J., a coach-builder, aged 42, was admitted to the hospital Feb. 10, 1913, complaining of shortness of breath.

Family History.—Father died of pneumonia, aged 52. Mother died at 47 of a "rheumatic heart."

Personal History.—There is no history of chorea or rheumatic fever. He contracted syphilis in 1889, for which he was treated with mercury over a period of eighteen months. During the winter of 1911 to '12 he had an attack of asthma. He has used alcohol in moderation, tobacco to the extent of 2 ounces a week.

Present Illness.—The patient attributes the onset of his present acute symptoms to the attack of asthma, which he had a year ago. Soon after this illness he began to suffer from shortness of breath and attacks of palpitation, which of late have grown more frequent and have been very distressing. Eight months ago he began to cough and from this time has had a persistent cough accompanied by a frothy expectoration, at times slightly streaked with blood. For the past two months he has noticed that he has voided less urine than usual. He has slept poorly.

Condition on Admission.—The patient is a stout man who looks older than he is. As he lies propped up in bed there is slight dyspnea. The respirations are 28. The chest moves but little and there is some impairment of resonance over the left base posteriorly. Over this area the respiratory sounds are weak. Sonorous and sibilant râles are heard over the entire chest. There is no clubbing of the fingers. The pulse is regular in force and rhythm, 100 per minute. The systolic blood-pressure is 186 mm. Hg. The liver is palpable 3 inches below the costal margin. There is slight edema of the feet. The temperature is normal. The specific gravity of the urine, on admission, was 1.030, with albumin present in excess and many hyaline and granular casts. The Wassermann reaction is positive.

Heart.—The apex-beat is visible and palpable in the sixth interspace, 6 inches from the midsternal line. The upper limit of cardiac dulness lies at the third interspace, to the right 1½ inches, and to the left 6 inches from the midsternal line. At the apex the first sound is loud and booming, accompanied by a soft systolic murmur; the second sound is short and valvular in character. The aortic second sound is accentuated, no murmurs are heard over the aortic area.

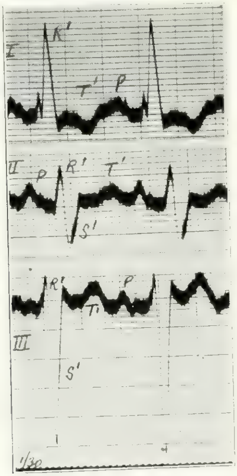

Fig. 15.—Electrocardiograms, Case 19. The P-R interval measures 0.2 second. In Lead I, the initial deflection R' is conspicuous as a tall peak of increased amplitude, with conspicuous notching. The final deflection T' is inverted, lying in the direction opposite to the deflection R'. In Lead II, R' and S' are both present and both show notching. The deflection S' is slightly the more conspicuous. The final deflection T' is upright, lying in a direction opposite to S'. In Lead III, R' is present, but the deflection S' is conspicuous as a deep depression of greatly increased amplitude. The final deflection T' is upright, in a direction opposite to the prominent S'. The increased amplitude of the initial deflections, the increased duration of the opening phases—the Q-R-S interval measures 0.12 second—and the direction of the final deflection T', in relation to R' and S', are apparent.

Subsequent History.—After a few weeks rest the acute symptoms were much relieved and the patient left the hospital. He was readmitted at a later date and died in the hospital. The P-R interval measures 0.18 and 0.2 second (two observations).

Case 20.—*Myocarditis, cardiac hypertrophy, aortic disease, cardiac failure and death.* (Electrocardiograms, Figs. 16 and 17.)

Patient.—D. H., a laborer, aged 38, was admitted to the hospital Feb. 25, 1913, complaining of shortness of breath and pain in the chest in the region of the heart.

Family History.—Mother is said to have died of "heart disease." No history of rheumatic fever in the family.

Personal History.—There is no history of any acute illness. The patient has never had chorea or rheumatic fever. He had syphilis fourteen years ago. He has used alcohol in moderation.

Present Illness.—The patient states that his present illness began five months ago, when he first noticed that he became short of breath after any slight exertion. This was soon followed by a sense of fulness and oppression in the chest. During the past month he has had attacks of pain in the chest referred chiefly to the region of the second and third interspaces on the left side. These attacks have latterly become more frequent, and at present the pain is quite constant. There has been no cough.

Condition on Admission.—The patient is well-built, slightly cyanotic and quite dyspneic. The pulse is regular in force and rhythm, typically water-hammer in character. Capillary pulsation is present. The liver is palpable below the costal margin.

Heart.—The point of maximum impulse is diffuse in the sixth interspace almost at the anterior axillary line. There is a palpable systolic thrill at the apex. The upper limit of cardiac dulness lies at the third rib, to the right 1¾ inches and to the left 6 inches from the midsternal line. Over the aortic area there is a double murmur, and passing upward a short systolic murmur is heard over the vessels in the neck. Passing downward the diastolic murmur becomes louder, being most intense over the third and fourth interspaces. As one passes outward toward the apex a rough rumbling murmur is heard just before and associated with doubling of the first sound, suggesting a Flint murmur.

Course.—After several weeks the patient's general condition so far improved that he was able to leave the hospital, being at the time of his discharge practically free from pain, though still dyspneic upon exertion. The area of cardiac dulness had slightly diminished, but otherwise the physical signs remained unchanged, though at this time the rumbling murmur heard at the apex was not clearly associated with reduplication of the first sound.

Readmission (May 15, 1913).—The patient was readmitted to-day, all his old symptoms being more pronounced. While he was in the out-patient department, the following note was made: Breathlessness more marked, slight cyanosis and excessive urobilin staining. There is a slight effusion at the base of the left lung. The liver is palpable at the level of the umbilicus.

Heart.—The apex-beat is diffuse in the sixth interspace. The limits of cardiac dulness are to-day at the third rib above, 2 inches to the right and 6½ inches to the left of the midsternal line. There is a systolic thrill at the apex and a systolic and a full diastolic rumble are heard over this area. Over the aortic and pulmonary areas there is a double murmur.

Course.—The patient's general condition grew gradually worse and he died in June, 1913.

Electrocardiograms.—This case is of more than usual interest in view of the widely varying degrees of heart-block recorded. The *P-R* interval ranged from 0.21 to 0.3 second. A comparison of the electrocardiographic curves recorded February 27 (Fig. 16) and again May 5, 1913, (Fig. 17), is most interesting and instructive.

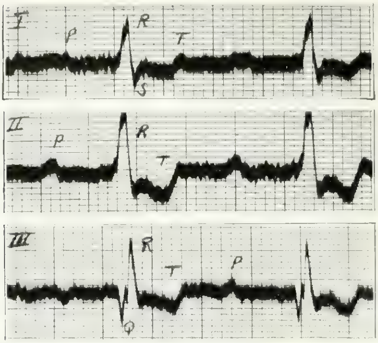

Fig. 16.—Electrocardiograms, Case 20. Before the development of the lesion involving the right branch of the auriculoventricular bundle. The *P-R* interval measures 0.3 second. In Lead I, *Q* is absent, *R* is prominent and already shows notching. *S* is inconspicuous. The final deflection *T* is upright. In Lead II, the initial deflection *R* is more prominent than in the first lead. The final deflection *T* is inverted. In Lead III, *Q* is conspicuous, *R* is prominent, and the final deflection *T* is again inverted. The increased *P-R* interval, the suggestive notching of the prominent deflection *R*, and the inversion of *T* are the sole signs of a disturbed mechanism, the curve is essentially that of cardiac hypertrophy.

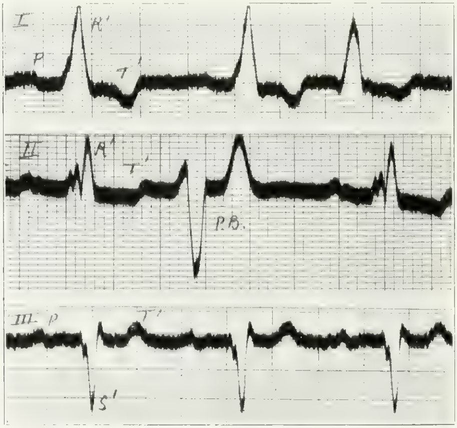

Fig. 17.—Electrocardiograms, Case 20. The *P-R* interval measures 0.22 second. The *Q-R-S* interval measures 0.12 second. In Lead I, the initial deflection *R'* appears as a tall wide peak, of greatly increased amplitude, with marked notching. The final deflection *T'* is inverted. The premature beat lies in the same direction as *R'*. In Lead II, the initial deflection *R'* appears as a conspicuously split summit. The final deflection *T'* is upright. The premature beat lies in a direction opposite to the conspicuous initial deflection *R'*. In Lead III, *R'* is absent, the conspicuous initial deflection *S'* appears as a deep depression, of increased amplitude, and with marked notching. The premature beats, it is seen, are in the same direction as the prominent initial deflection *R'* in Lead I, and in the opposite direction in Lead II.

These two figures illustrate again, in a striking way, the difference between the electrocardiogram obtained as a result of simple cardiac hypertrophy, and that due to defective conductivity.

The earlier physiological electrocardiogram for this patient, obtained in the light of a full knowledge of the degree of cardiac hypertrophy present, could not be confused with the aberrant complex obtained later, after the development of the lesion involving the conduction of the right branch of the bundle.

Case 21.—*Myocarditis, arteriosclerosis, aortic disease and cardiac failure.* (Electrocardiograms, Fig. 18.)

Patient.—J. M., a porter, aged 39, was first seen June 5, 1913, complaining of palpitation of the heart and shortness of breath.

Family History.—Negative.

Personal History.—There is no history of any acute illness. The patient has not had rheumatic fever. There is a history of syphilis fourteen years ago, for which he was under treatment nine months. He uses alcohol and tobacco in moderation.

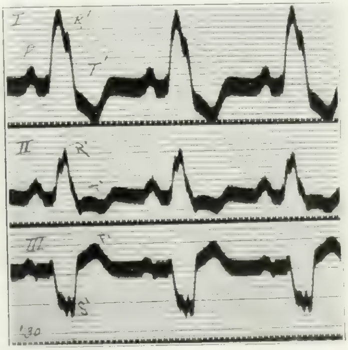

Fig. 18.—Electrocardiograms, Case 21. The P-R interval measures 0.17 second. The Q-R-S interval measures 0.2 second. In Lead I, the initial deflection R' is conspicuous as a tall, broad summit with marked notching. The final deflection T' is conspicuous and inverted, lying in a direction opposite to the summit R'. In Lead II, the initial deflection R' is again conspicuous as a summit of increased height and duration, with marked notching. The final deflection T' is inverted, lying in a direction opposite to the prominent summit R'. In Lead III, the initial deflection S' is conspicuous as a deep, broad depression with marked notching. The final deflection T' is upright in a direction opposite to the conspicuous S'. The increased amplitude of the initial deflections, the increased duration of the opening phases, the direction of the final deflection T' in relation to the prominent initial deflections R' and S', the conspicuous notching, and the diphasic character of the complex are apparent.

Present Illness.—The patient states that for the past seven years he has had palpitation of the heart on slight exertion. Beginning in August, 1912, he first noticed that he quickly became very short of breath after any unusual effort. He has had occasional pains in the right shoulder, but nothing that could suggest acute rheumatic fever. Under medical advice he has been doing little work for the past three months, and states that his general condition has improved considerably.

Condition on Admission.—The patient is thin and rather poorly nourished. He is slightly cyanotic and quite breathless on exertion. The pulse is regular in force and rhythm, except for an occasional extrasystole. The arteries are moderately thickened. The systolic blood-pressure is 120 mm. Hg.

Heart.—The point of maximum impulse is in the fifth and sixth interspaces. The limits of cardiac dulness lie at the third interspace above, and $2\frac{1}{2}$ and 5 inches to the right and left of the midsternal line, respectively. There is a well-marked shock over the left side of the cardiac area and considerable pulsation in the second right interspace. There is a systolic thrill at the base and a pronounced diastolic murmur at the aortic cartilage. There is a suggestive Flint murmur at the apex. The liver is just palpable at the costal margin. The Wassermann reaction is positive.

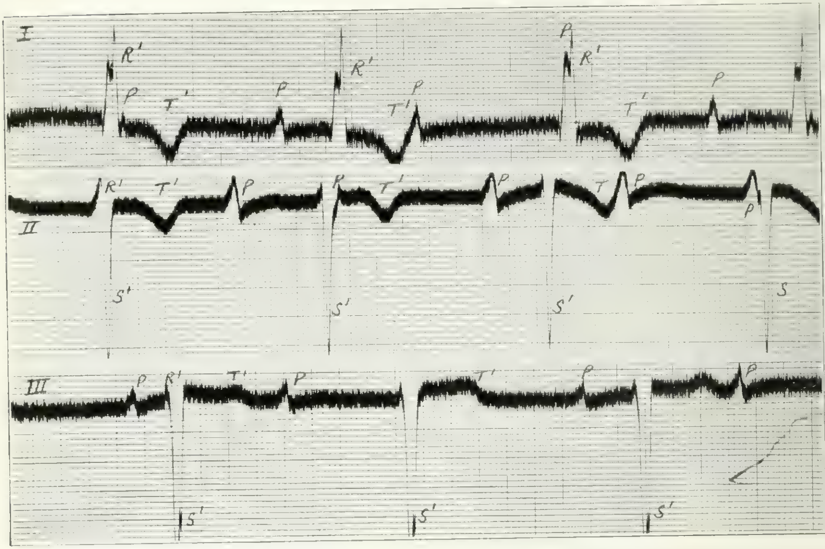

Fig. 19.—Electrocardiograms, Case 22. Note the complete independence of the auricular and ventricular rhythms. The ventricular rate is 39, the auricular rate approximately 60. In Lead I, the initial deflection R' is conspicuous as a tall summit, with marked notching of increased amplitude and of slightly increased duration. The final deflection T' is conspicuous and inverted, lying in a direction opposite to the prominent summit R'. The auricular summit P falls just at the conclusion of the deflection R' in the first complex of the figure, and obscures the diphasic character of the complex as seen in the second and third ventricular deflections. In Lead II, the initial deflection R' is present but not prominent. The deflection S' is conspicuous as a deep depression of greatly increased amplitude. The final deflection T' is inverted, lying in the same direction as the prominent deflection S'. In Lead III, R' is just seen. The initial deflection S' is again conspicuous as a deep depression of greatly increased amplitude, with notching near the base. The final deflection T' is upright in a direction opposite to S'. The Q-R-S interval exceeds 0.1 second in all three leads. The premature beats recorded in this case were in a direction opposite to the aberrant deflections in Leads I and III, and hence arose from the right and basal portion of the ventricle.

CASE 22.—*Congenital pulmonary stenosis, cardiac hypertrophy and complete auriculoventricular heart-block.* (Electrocardiograms, Fig. 19).

Patient.—E. N., aged 27, a domestic, was first seen March 12, 1913, complaining of shortness of breath, of a "winter cough" for as far back as she can remember, and latterly of pain in the chest about the heart.

Family History.—Negative.

Personal History.—Apart from the statement, given above, of shortness of breath, and of the history of a "winter cough" for many years, there is absolutely no other history of any acute illness. The patient has never had scarlet fever, chorea, rheumatic fever or tonsillitis. Careful questioning fails to elicit any history at all suspicious of a syphilitic infection. She states that, as a young girl at school, she frequently used to "feel faint," but that she never fell down or lost consciousness. She has had no such sensations of faintness now for many years. She has had no palpitation or sense of disturbance as of sudden stoppage of the heart. There is no history of any giddiness or dizziness in recent years.

Present Illness.—The patient has been in domestic service for the past seven years, doing hard, general work, which often involved heavy lifting. She first began to notice more aggravated shortness of breath about a month ago (February 12), and found that she could not do her work as usual without quickly becoming very breathless and fagged out. Three weeks ago (February 19) she first complained of pain in the chest, in the region of the heart, of sudden onset, quite sharp, and described as jumping in character. This pain is not constant, but comes on quite frequently three to eight, or more times a day. The pain has never been referred to the left shoulder or down the left arm.

Condition on Admission.—The patient is slightly built and rather poorly nourished. There is considerable cyanosis of the lips and hands, but no clubbing of the fingers. The pulse is of small volume, regular in force and rhythm, 39 to the minute.

Heart.—The point of maximum impulse lies in the fifth interspace in the nipple line, but there is also a pulsation in the anterior axillary line. The upper limit of cardiac dulness lies at the third interspace, to the right 1¾ inches, and to the left 5¼ inches from the midsternal line. There is a pronounced shock over the precordium. There is a well-marked thrill palpable over the upper precordium, and heard at its maximum over the second left cartilage. At the apex the first sound is loud, followed by a soft systolic murmur. The second sound is reduplicated. Over the aortic area there is a faint systolic murmur. The respiratory rhythm is almost synchronous with the ventricular rate, but tracings show that this is not constant.

Course.—The patient has been seen quite regularly, at weekly intervals. Her general condition has improved. By May 19 she was quite free from any attacks of pain, and the extreme breathlessness, for which she first sought relief, had been greatly relieved. May 26 she felt so much better that she asked to be allowed to return to work.

Electrocardiograms.—This case is of more than unusual interest because of the presence of complete auriculoventricular heart-block together with a lesion involving the conductivity of the right branch of the auriculoventricular bundle. It is the single instance of complete auriculoventricular heart-block in our series, and illustrates in an incomparable way, the association of lesions involving the main stem and one of its divisions.

CONCLUSIONS

1. In the presence of lesions involving the conductivity of the branches of the auriculoventricular bundle, a distinct and characteristic type of electrocardiogram is obtained. To the ventricular contractions on which these depend the term *aberrant* may be applied.

2. This type of electrocardiogram is frequently associated with aortic valve disease; it is distinct from that of hypertrophy predominant in one ventricle.

3. Bundle-branch defects are usually accompanied by defects in the main trunk, suggesting that the junctional tissues as a whole have a special pathology.

4. The evidence in our possession is too slight to admit of any definite conclusions as to the relation between lesions of the bundle branches and the occurrence of extrasystoles.

5. The electrocardiographic pictures of aberrant beats are probably of considerable prognostic importance.

I wish to express my indebtedness to Dr. Thomas Lewis, of London, for his kindness in placing his notes and records at my disposal; for many valuable suggestions and the courteous aid received from him in the preparation of this report.

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THE VALUE OF HEXAMETHYLENAMIN AS AN INTERNAL ANTISEPTIC IN OTHER FLUIDS OF THE BODY THAN URINE *

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In previous communications I have presented a method for the quantitative estimation of formaldehyd in the urine of patients receiving hexamethylenamin by mouth,[1] and the results of a study with this method of the value of the internal use of hexamethylenamin as a urinary antiseptic.[2] This study on the urine clearly indicates that the conversion of hexamethylenamin into formaldehyd is a simple chemical process which will readily occur in an acid medium, but will not occur in an alkaline medium. It also shows that the amount of this conversion is dependent on the degree of urinary acidity, the duration of exposure to the action of this acidity and the percentage concentration of the drug in it. These facts have a significant bearing on the justification of the wide-spread therapeutic use of hexamethylenamin for other than vesical conditions. It has been recommended as an antiseptic for practically all of the body fluids, the only basis for which, aside from clinical observations, is the presence of the drug in these fluids after internal administration.

Although Butlerow[3] had prepared hexamethylenamin more than thirty years before, Nicolaier,[4] in 1894, introduced it into medicine, and demonstrated formaldehyd in the urine as its decomposition product. Richardson,[5] in 1899, confirmed Nicolaier's findings. These observations immediately popularized the drug as a urinary antiseptic. In 1907, Bucura[6] found free hexamethylenamin in human milk. A year later

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* Read Jan. 5, 1914, before the Johns Hopkins Medical Society, Baltimore.

[1] Hinman, Frank: Tr. Am. Assn. Gen.-Urin. Surg., May 7, 1913.

[2] Hinman, Frank: An Experimental Study of the Antiseptic Value in the Urine of the Internal Use of Hexamethylenamin. Jour. Am. Med. Assn., 1913, lxi, 1601.

[3] Butlerow: Ann. d. Chem. u. Pharm., 1860, cxv, 330.

[4] Nicolaier: Deutsch. med. Wchnschr., 1895, xxi, 541.

[5] Richardson: Jour. Exper. Med., 1899, iv, 19.

[6] Bucura: Arch. f. exper. Path. u. Therap., 1907, iv, 398.

Crowe[7] showed that it is excreted in the bile, pancreatic juice and synovial and cerebrospinal fluids, and he recommended its prophylactic and curative value in diseases of the meninges of the brain and spinal cord. Barton,[8] in 1910, found hexamethylenamin in secretions of the middle ear, and since then much has been written relative to its antiseptic value in otitis media. In the same year Hanzlik[9] showed that it is excreted in saliva, and a year later Armstrong and Goodman[10] found it in the sputa of tuberculosis and of pneumonia. About the same time Gradle[11] demonstrated its presence in the anterior chamber of the eye, and in 1912 Whitman[12] found it in both the aqueous and vitreous humors. These findings have been repeatedly confirmed. All authorities are, therefore, agreed that hexamethylenamin is present after internal administration, in practically every fluid of the body.

Because of the ready conversion into formaldehyd in the urine, it has been assumed by some investigators that it acts in a similar manner in these other fluids, while other observers have presumably regarded hexamethylenamin itself as of antiseptic value. In the literature there is no evidence of free formaldehyd having been demonstrated definitely in any of these body-fluids (urine excepted). Hanzlik[9] was unable to find it in the saliva; Schmid and Schroeter[13] failed to find it in human milk; Burnam[15] could not demonstrate it in the cerebrospinal fluid or bile, and more recently Hanzlik and Collins[15] have stated positively that free formaldehyd is never present in saliva, milk, bile, cerebrospinal, synovial, pericardial and pleural fluids of man or in the vitreous or aqueous humors of animals. The apparent confusion on this point is due to the character of tests employed. In those cases in which free formaldehyd has been reported as present in these fluids after the ingestion of hexamethylenamin, the tests that have been used employ strong acids, which, by their action on the hexamethylenamin, liberate formaldehyd, which then reacts.

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7. Crow, J. S.: Johns Hopkins Hosp. Bull., 1908, xix, 109; ibid., xx, 102.

8. Barton, W. M.: The Elimination of Hexamethylenamin by the Mucous Membrane of the Middle Ear, Jour. Am. Med. Assn., 1910, liv, 871.

9. Hanzlik, P. J.: The Excretion of Hexamethylenamin in the Saliva, Jour. Am. Med. Assn., 1910, liv, 1940.

10. Armstrong, J. J., and Goodman, E. H.: The Excretion of Salicylic Acid and Hexamethylenamin in the Sputum, Jour. Am. Med. Assn., 1911, lvi, 1553.

11. Gradle, W. S.: Ophth. Rec., March, 1911.

12. Whitman: Arch. Ophthalmol., 1912, xli, 604.

13. Schmidt and Schroeter: Centralbl. f. Physiol. u. Path. d. Stoffwechsel, 1910, v, 129.

14. Burnam, C. F.: An Experimental Investigation of the Value of Hexamethylenamin and Allied Compounds, The Archives Int. Med., 1912, 324.

15. Hanzlik, P. J., and Collins, R. J.: Hexamethylenamin: The Liberation of Formaldehyd and the Antiseptic Efficiency under Different Chemical and Biological Conditions, The Archives Int. Med., 1913, xii, 578.

As an example of this may be cited the results of Ibrahim,[16] who in 1910 presented a bacteriological study of the cerebrospinal fluid with reference to the inhibitory action of hexamethylenamin on different organisms (*Staphylococcus aureus, Bacillus coli, B. typhi abdominalis* and *B. pyocyaneus*) with these conclusions:

1. After the internal administration of hexamethylenamin this can be demonstrated in the cerebrospinal fluid of infants.

2. Hexamethylenamin in solution in cerebrospinal fluid forms, on standing at 37 C., formaldehyd.

3. Hexamethylenamin gives in the cerebrospinal fluid at body temperature bactericidal action.

4. On the grounds of this activity it appears justified to administer hexamethylenamin as a therapeutic measure in all forms of serous and purulent meningitis.

Ibrahim did not recognize the significance of acidity in the liberation of formaldehyd. He used three tests: Nicolaier's[17] *Bromwasserprobe*, Jorrison's test with the use of acetic acid,[18] and Hehner's test (sulphuric acid). The first is a test for hexamethylenamin and the other two, because of the acid used, are unreliable. With regard to the antiseptic findings the bacterial counts are not very convincing, and I was unable to confirm them in three cases in which, after the addition of about 0.05 gm. hexamethylenamin to 5 c.c. of spinal fluid, there was no inhibition of either *Staphylococcus aureus* or *Bacillus coli* after seventy-two hours' incubation, as shown by the count after transferring one oese to an agar-plate, although the delicate tests (phloroglucin and amidol) for formaldehyd were present.

The importance of acidity to the decomposition of hexamethylenamin has but just recently been recognized. Wiggs[19] suggested its influence in the urine in 1910. Jordan,[20] a year later, reported that formaldehyd was not found in alkaline urines, and recently studies by Smith,[21] Hanzlik and Collins[15] and myself[2] have independently demonstrated the importance of the degree of urinary acidity in the use of hexamethylenamin as a urinary antiseptic. The excellent paper of Hanzlik and Collins appeared not long ago, and, since it is in accord largely with the present study, a few of their conclusions will be given, and are as follows:

> Alkalies prevent, while acids facilitate the liberation of formaldehyd from hexamethylenamin in all body fluids.

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[16] Ibrahim: Med. Klin., 1910, p. 48.

[17] Nicolaier: Ztschr. f. klin. Med., 1899, xxxviii, 350.

[18] Jorrison: Chem. Ztz., 1897, 290.

[19] Wiggs: South. Med. Jour., December, 1910.

[20] Jordan: Biochem. Jour., 1911, v, 274.

[21] Smith, G. G.: Bost. Med. and Surg. Jour., May 15, 1913.

The liberation of formaldehyd from hexamethylenamin in pathological fluids obeys the same laws as in other solutions, that is, it can only occur in acid reaction.

After administration, hexamethylenamin is present, but does not liberate free formaldehyd in blood, cerebrospinal, pleural, pericardial and synovial fluids, vitreous and aqueous humors, and urine when truly alkaline.

The beneficial therapeutic effects of hexamethylenamin depend on the liberated formaldehyd. Such effects are to be expected principally, if not always, in acid urine only.

The present work embodies the testing for formaldehyd of both normal and pathologic fluids of patients being fed hexamethylenamin with a study of the action of these fluids *in vitro* toward the liberation of formaldehyd when subjected to infection. The main question at issue was to determine whether infection could alter the reaction of these normally alkaline fluids sufficiently to produce the liberation of formaldehyd, and, if so, whether there would be enough liberated to produce antisepsis.

ANTISEPTIC VALUES OF FORMALDEHYD AND HEXAMETHYLENAMIN

A review of the work of other investigators and my own experiments[1] indicates that formaldehyd is a slow and a relatively weak germicide, but that, up to certain dilutions, it exerts a powerful inhibitory influence on bacterial development. This power of inhibition varies slightly with different organisms. A dilution of liquor formaldehydi of about 1:16,000 will cause complete inhibition of the growth of *Bacillus typhosus* for twenty-four hours; a dilution of about 1:6,000 will completely kill the organism in that time; about 1:30,000 dilution will partially restrain its growth, while a 1:40,000 dilution has no apparent effect unless the results are shown by means of plating and a systematic bacterial count when a slight diminution in the count is obtained. Higher dilutions have no inhibitory effect.

Hexamethylenamin has been shown repeatedly (Burnam, Jordan, Hanzlik and Collins) to have no germicidal or antiseptic power. Hanzlik and Collins found that hexamethylenamin, to which 0.5 per cent. ammonium hydroxid had been added to prevent the liberation of formaldehyd, in as strong a dilution as 1:50 did not inhibit the growth of the organisms studied. In my experiments bacteria (*B. typhosus, B. coli, M. pyogenes aureus*) grew as readily in a slightly alkaline broth to which hexamethylenamin had been added in the proportion of 1:100 as in normal broth.

It is seen, therefore, that hexamethylenamin is of value as an antiseptic only after its conversion into formaldehyd, which must be present in the proportion, at least, of about 1:30,000.

TESTS EMPLOYED FOR FORMALDEHYD AND HEXAMETHYLENAMIN

Four different tests were made use of in the examination of material. Hehner's test[22] was used to show the presence of hexamethylenamin. It is really a test for formaldehyd, but the strong sulphuric acid used in the test quickly converts the hexamethylenamin into formaldehyd, which then reacts, so that it is given equally well by both drugs. The amidol[23] and Jorrison's[18] phloroglucin tests were used to detect small amounts of formaldehyd not shown by the Rimini test. The amidol test, although very delicate, is not particularly reliable, and is not applicable to all fluids. The phloroglucin test is both delicate and reliable. Neither test is given by hexamethylenamin. Both are qualitative tests only. Rimini's[24] test was modified so as to be used for quantitative estimation[1] of formaldehyd, for which it is reliable up to dilutions of about 1:60,000. It is not given by hexamethylenamin. If formaldehyd is present in less amount than 1:60,000, it can be of no practical importance inasmuch as it would not be antiseptic; but the amidol and phloroglucin tests would show even minute quantities (up to 1:10,000,000). With these tests it is possible to determine the presence or absence of both hexamethylenamin and of formaldehyd, to determine whether hexamethylenamin is present alone and if formaldehyd is present, to estimate the quantity up to 1 : 60,000.

EXAMINATION OF NORMAL AND PATHOLOGIC FLUIDS

The material for examination consists of that from eleven cases of cerebrospinal and ventricular fluids, four cases of otitis media, two cases of empyema, one case of pelvic abscess, six normal blood-serums, two cases from which normal bile was obtained, three from which sweat and five from which saliva was collected. This material may seem small in amount from which to draw conclusions, but the main object in view was experimental and not clinical. Each fluid was subjected to many different tests with particular reference to changes in reaction and the influence of these changes on the liberation of formaldehyd. With two exceptions all patients had been given hexamethylenamin by mouth before the fluids were collected. In no case was free formaldehyd found. All showed the presence of hexamethylenamin. After the conversion of this hexamethylenamin with acid there was in no case enough formaldehyd liberated to furnish antisepsis. These findings will be outlined briefly and tabulated.

Cerebrospinal Fluid.—The spinal or ventricular fluid was obtained by lumbar and ventricular puncture in several cases and tested as shown

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[22] Hehner: Abstr., Lond. Chem. Soc., 1896, A, ii, 583.

[23] Referred to in Allen: Commercial Organic Chemistry.

[24] Rimini: Chem. Zentralbl., 1898, i, 1152; abstr., Jour. Soc. Chem. Industr., 1898, 697.

TABLE 1.—EXAMINATION OF CEREBROSPINAL FLUID

Case	Diagnosis	Material and Treatment	Tests*			
			Date	Hehner	Rimini	Amidol or Phlorogluci
1	Tuberculous meningitis.	Hexam. 15 gr., t. i. d., p. c., for several days. Lumbar puncture, 11 c.c. fluid	4/24	+	—	—
		Crystals of acid sodium phosphate added to 3 c.c..................	4/24 4/26	+	—	+
		5 c.c. inoculated with *M. pyo. aur.*...	4/24			
		Incubated at 37 C. for six days......	4/30	+	—	+
2	Tuberculous meningitis.	Hexam. 20 gr., t. i. d., p. c. Lumbar puncture	4/26	+	—	—
3	Lues.	Hexam. 20 gr., q. 2 h., two days. Lumbar puncture		+	—	—
		Crystals of Na_2HPO_4 added to 5 c.c. after twenty-four hours...........		+	†	+
4	Medical.	Hexam. 20 gr., q. h., added 4 doses. Lumbar puncture		+	—	—
		4 c.c. inoculated with *B. coli* after forty-eight hours		+	—	+
5	Medical.	Hexam. 20 gr., q. h., added 4. Lumbar puncture		+	—	—
6	Hydrocephalus in child.	Hexam. 5 gr., q. h., added 8. Ventricular puncture		+	—	—
		5 c.c. inoculated with broth culture of meningococcus after fourteen days' incubation		+	—	+
7	Medical.	No hexam. by mouth. Lumbar puncture		—	—	—
		Hexam. 1 gr. added to 3 c.c. and tested after standing forty-eight hours		+	—	—
		Crystals of Na_2HPO_4 added to 3 c.c. with hexam. 1 gr. and tested after twenty-four hours		+	‡	—
8	Hydrocephalus in child.	Hexam. 40 gr., q. d., for three days. Lumbar puncture		+	—	—
		Ventricular puncture		+	—	—
		Above after standing three days.....		+	—	—
9	Hydrocephalus	Hexam. 5 gr., t. i. d., p. c., for two weeks. Lumbar puncture		+	—	—
		Ventricular puncture		+	—	—
10	Hydrocephalus in child.	Hexam. 5 gr., t. i. d. Ventricular puncture		—	—	—
		8 c.c. made strongly acid with H_2SO_4 after twenty-four hours		—	—	
11	Meningitis.	Hexam. 40 gr., in day; 75 gr. after midnight. Lumbar puncture at 10 a. m.		+	—	—
		5 c.c. inoculated with *M. pyo. aur.* incubated five days		+	†	—

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* In this and the following tables, + = positive, —, negative.
† 1:60,000. ‡ 1:20,000.

in Table 1. Hexamethylenamin was present in all of the cerebrospinal fluids with the one exception. In Case 10 the fluid obtained by lumbar puncture was negative to Hehner's test, and the addition of sulphuric acid failed to render the test positive for formaldehyd. In none of these fluids in which hexamethylenamin was present following the administration of the drug by mouth was free formaldehyd found. After inoculation of these fluids containing hexamethylenamin with the meningococcus, *M. pyogenes aureus* or *B. coli*, formaldehyd was not liberated in amounts sufficient to give the Rimini test (1 : 60,000), although after several days' incubation they were all positive to the delicate amidol or phloroglucin tests for formaldehyd. The addition of acid sodium phosphate to the fluid in one case (Case 3) in which the patient had received enormous doses of hexamethylenamin, 20 grains every two hours, caused after twenty-four hours the liberation of formaldehyd in about 1 : 60,000 dilution. Hexamethylenamin added directly to these fresh fluids was not decomposed, and the subsequent inoculation of these concentrated solutions in no case caused a liberation of formaldehyd in a greater amount than 1 : 60,000.

TABLE 2.—EXAMINATION OF PURULENT DISCHARGES IN OTITIS MEDIA

Case	Material and Treatment	Tests		
		Hehner	Rimini	Amidol or Phloroglucin
1	Hexam., gr. 5, q. 2 h., added doses 6. Discharge obtained by syringing out the ear with small amount of sterile water	—	—	—
2	As above	—	—	—
3	As above	—	—	—
4	As above	—	—	—
5	As above	—	—	—

Purulent Discharge in Otitis Media.—The material was obtained in cases of acute otitis media by syringing out the ear with as small an amount of sterile water as possible. With the exception of one case, which gave a positive Hehner's test for hexamethylenamin, all failed to show either hexamethylenamin or formaldehyd. The findings are not accurate, inasmuch as the discharges were necessarily diluted before being tested, but the failure to find even minute quantities of either drug are significant. The findings are grouped in Table 2.

Pus of Empyema.—Two patients with empyema were given hexamethylenamin for a few days, and at operation the pus was obtained and examined as is shown in Table 3. All tests were uniformly negative, showing the absence of both hexamethylenamin and formaldehyd; but the pus was strongly acid in reaction, and when hexamethylenamin was added to it *in vitro* it was quickly decomposed into formaldehyd.

Pelvic Abscess and Pus-Tube.—One patient was given hexamethylenamin, 20 grains, after each meal for two days before an operation for pus-tubes and a pelvic abscess. The pus obtained at operation was examined with negative results for all tests. The reaction of the pus was strongly acid, 9.7 c.c. tenth-normal sodium hydroxid to 10 c.c., and when examined four hours after the addition of 5 grains of hexamethylenamin to 40 c.c. of it, formaldehyd was present in the proportion of 1 : 10,000.

Blood-Serum.—Venous puncture was done in six cases in which the patients were being given a routine dosage of 15 grains of hexamethylenamin after each meal, and the serum after separation was tested with negative results in all cases for formaldehyd, but positive in all for hexamethylenamin. The addition of acid sodium phosphate to these serums in no case caused a liberation of formaldehyd in sufficient amount to give a 1 : 60,000 test, although the more delicate formaldehyd tests were uniformly present after this treatment.

TABLE 3.—EXAMINATION OF PUS OF EMPYEMA

Case	Material and Treatment	Reaction	Test		
			Hehner	Rimini	Amidol or Phloroglucin
1	Hexam., 10 gr., t. i. d., p. c. Operation after two days and 600 c.c. of pus obtained which showed a pure culture of pneumococcus......	13.6 c.c. Tenth-normal sodium hydroxid to 10 c.c.	—	—	—
	Hexam. added to 200 c.c. of above examined after twenty-four hours................	....	+		+
	(Culture made from this on the seventh day was negative) after seven days...........	After 7 days.	+	†	—
2	Hexam., 15 gr., t. i. d., p. c. Operation three days, 300 c.c. pus obtained...........	1.6 c.c.	—	—	—

* 1 : 10,000. † 1 : 7,000.

Sweat.—Two patients receiving hexamethylenamin, 15 grains, after each meal, were placed in a sweat-cabinet, their perspiration collected[25] and examined with positive results in both cases for hexamethylenamin. The Rimini test was negative in both. Unfortunately, the more delicate phloroglucin test was not tried in these cases. Sweat is slightly acid in reaction, and possibly the small amount of hexamethylenamin present had been converted into formaldehyd, which would also give the delicate Hehner's test. It was not, however, present in anything like an antiseptic strength.

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[25] Through the kindness of Dr. Harry Plaggemeyer.

Saliva.—The saliva was collected from five patients receiving a routine dosage of 15 grains after each meal. A positive Hehner's test was obtained in all but one case, but the other tests were all uniformly negative.

Bile.—Hexamethylenamin when taken by mouth is excreted in the bile. Free formaldehyd, however, is not found. After the addition of hexamethylenamin to sterile bile *in vitro* even in the proportion of 1 : 100, it is not decomposed so long as the bile is kept sterile. Infection of these concentration bile solutions causes a liberation of formaldehyd, but in the two cases tested not more than 1 : 60,000 was found. There has been no opportunity to examine the contents of the gall-bladder in cases of infection after feeding hexamethylenamin. It is possible that in cholecystitis or empyema of the gall-bladder its contents may have a sufficient acidity readily to convert the hexamethylenamin excreted into it.

Hexamethylenamin in Standard Broth.—In order further to test the influence of infection on the reaction of fluids and on the subsequent liberation of formaldehyd, known dilutions of hexamethylenamin were made up in standard broth, inoculated with various organisms and tested after certain periods for changes in reaction and for free formaldehyd. The findings are given in Table 4. The changes in reaction are slight in all cases, so much so that in no case was more than 1 : 60,000 formaldehyd found after the growth of an organism in a 1 : 1,000 hexamethylenamin solution for as long as five days, and the growth of the organism was in no case inhibited.

SUMMARY OF EXAMINATION OF NORMAL AND PATHOLOGIC FLUIDS

The amount of decomposition of hexamethylenamin into formaldehyd is so clearly dependent on acidity and concentration that the problem resolves itself into a determination of these factors. None of these fluids are normally acid, and whatever tendency there is for them to become acid is being continually counteracted by the alkaline circulation. On the other hand, the amount of hexamethylenamin present in these fluids has been found to be relatively small, which is no doubt due to the fact that it is rapidly eliminated by the kidneys and is not given an opportunity to accumulate. Formaldehyd, if it is liberated within the body, is

TABLE 4.—TESTS OF HEXAMETHYLENAMIN IN STANDARD BROTH

Organism	Dilution	24 Hours			48 Hours			72 Hours			120 Hours		
		Reaction*	Formaldehyd†		Reaction*	Formaldehyd		Reaction*	Formaldehyd		Reaction*	Formaldehyd	
			Rimini	Amidol		Rimini	Amidol		Rimini	Amidol		Rimini	Amidol
B. coli	1:1,000	Alk. 1	—	+	Acid 2	—	+	Acid 4	‡	+	Acid 4	‡	+
	1:10,000	Alk. 1	—	+	Acid 4	—	+	Acid 6	—	+	Acid 6	—	+
B. typhosus ...	1:1,000	Acid 4	‡	+	Acid 6	‡	+	Acid 6	‡	+	Acid 6	‡	+
	1:10,000	Acid 2	—	+	Acid 4	—	+	Acid 6	—	+	Acid 6	—	+
B. proteus vulgaris	1:1,000	Acid 1	—	+	Acid 4	—	+	Acid 4	‡	+	Acid 6	‡	+
	1:10,000	Acid 2	—	+	Acid 4	—	+	Acid 6	—	+	Acid 6	—	+
Streptococcus pyogenes aureus	1:1,000	Alk	—	—	Alk.	—	—	Acid 2	—	+	Acid 8	‡	+
	1:10,000	......	..	..	......	..	..	......	..	..	......	..	.
Meningococcus.	1:1,000	Alk.	—	—	Acid 2	—	+	Acid 4	—	+	Acid 4	—	+
Alkaligenes ...	1:1,000	Alk.	—	—	Alk.	—	—	Alk.	—	—	Alk.	—	—
Control typhoid	0	Alk.	—	—	Acid 2	—	—	Acid 4	—	—	Acid 8	—	—
Contral hexamethylenamin	1:1,000	Alk.	—	—	Alk.	—	—	Alk.	—	—	Alk.	—	—
Control urine..	1:1,000	Acid	‡	+	Acid 2.6 §	‡	+	Acid 2.6 §	‡	+			

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* The numerals under "Alk." or "Acid" indicate the number of drops of tenth-normal hydrochloric acid (alk.) or tenth-normal sodium hydroxid (acid) necessary, respectively, to neutralize 10 c.c. of the solution with phenolphthalein as indicator.

† In the tests, + means positive and — negative.

‡ Percentage of formaldehyd. 1:60,000.

§ The figures in the lowest column under "Acid" indicate the number of cubic centimeters of tenth-normal sodium hydroxid needed to an irritant, and as such is not tolerated by the organism. Maguire[26] found that intravenous injection of formaldehyd into animals produced gastric irritation with ulcer formation, hematuria and hemoglobinuria and death. Several of my patients were fed liquor formaldehydi (in dilution of 1:3,000, 6 ounces every three hours), and afterward their blood and urine were repeatedly found to be negative to all tests for both hexamethylenamin and formaldehyd, showing that the body can in some way burn up these small amounts. The fate of the formaldehyd which gets into the circulation is uncertain. There is experimental evidence to suggest that when not excreted by the kidneys it is neutralized into a harmless polymer and possibly hydrolyzed in the liver into one of the sugars. The conditions, therefore, for the decomposition of hexamethylenamin in antiseptic amounts are seldom, if ever, realized in these alkaline body-fluids.

From these facts and from the uniform negative findings on direct examination it is evident that hexamethylenamin can be of no value in the alkaline or neutral fluids of the body, such as found on the serous surfaces in general. This will be true even when enormous doses of the drug are administered, which is shown by no conversion occurring in these fluids when large amounts of the drug are added directly to them. Hexamethylenamin, therefore, can be of no prophylactic benefit in any of the body-fluids except those that are normally acid, and the only three fluids of this character are the urine, sweat and gastric juice.

The question of the influence of infection on these alkaline fluids relative to the liberation of formaldehyd is more difficult to answer. The examinations for formaldehyd of the pathologic fluids of patients given hexamethylenamin by mouth were all uniformly negative. After the subsequent addition of hexamethylenamin to these fluids, with the exception of localized accumulations of pus, no decomposition of this into formaldehyd was found. In local accumulations of pus, as in empyema or abscesses, this may have a pronounced acidity, and the addition of hexamethylenamin even in amounts of 1:10,000, to this pus quickly liberates formaldehyd. *In vivo,* however, these pus-pockets are apparently so well walled off that very little of the hexamethylenamin in the blood finds its way into them. If hexamethylenamin did enter in at these local areas, the formaldehyd formed there would naturally have as ready access to the circulation and would be carried off as fast as formed, so that no accumulation for antiseptic purposes would occur. The gallbladder, in those infections in which its contents become acid, may be a possible exception.

The subsequent inoculation with organisms of fluids obtained from patients taking hexamethylenamin by mouth, even on seven days' incu-

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26. Maguire: Med. News, 1903, lxxxiii, 393.

bation, in no case liberated formaldehyd in antiseptic amounts, although the more delicate tests of those showing formaldehyd up to 1 : 10,000,000 were sometimes obtained. And after the addition of as much as 1 : 1,000 hexamethylenamin to these fluids and then their inoculation, formaldehyd was liberated only after several days in 1 : 60,000 amounts. The inoculation of broth solutions of hexamethylenamin in no case showed greater conversion than 1 : 60,000, and then only after seventy-two hours. Infection of these fluids *in vitro,* therefore, even under the most favorable circumstances, that is, when hexamethylenamin has been added in as high a dilution as 1 : 1,000, a concentration that would never obtain *in vivo,* does not produce sufficient change in reaction to form formaldehyd in antiseptic strength. Furthermore, those fluids containing hexamethylenamin after its ingestion by mouth, when made strongly acid with acid sodium phosphate or sulphuric acid, did not contain hexamethylenamin in amounts to liberate more than 1 : 60,000 formaldehyd, showing that hexamethylenamin was not present in sufficient concentration to furnish antisepsis even should all present be decomposed.

It is reasonable to assume, therefore, that infection in the body does not change the reaction of the body-fluids into which hexamethylenamin is secreted sufficiently to cause its conversion in antiseptic amounts. In case of localized accumulations of pus of marked acidity, hexamethylenamin does not gain access in amounts to be of value, and in the case of other infection in communication with the circulation, the small amount of formaldehyd formed is quickly taken up and metabolized or excreted by the kidneys.

CONCLUSIONS

Hexamethylenamin is dependent on the liberation of formaldehyd for its antiseptic value.

Hexamethylenamin is not converted into formaldehyd in any of the normal alkaline fluids of the body; therefore, it can be of no prophylactic value in any of these fluids.

After some infections of these fluids there may be under certain conditions a change in reaction sufficient to produce slight liberation of formaldehyd, but it was not possible to show that there would be enough to give antisepsis.

In localized infections of pronounced acidity, hexamethylenamin is not taken into them from the circulation in amounts to furnish formaldehyd in antiseptic strength (the gall-bladder, possibly, excepted).

The therapeutic use of hexamethylenamin as an internal antiseptic is justified, experimentally, for urinary conditions alone, and then only when it is excreted into an acid urine.

HEXAMETHYLENAMIN *

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Hexamethylenamin is widely used as an antiseptic to prevent and to combat various infections of the serous cavities and blood as well as those of the urinary tract, the wide range of application being due to the striking effects obtained in some cases of cystitis and allied conditions, as well as to the great penetrability of the drug, which after ingestion can be found in every fluid of the body.[1] These facts, as well as the possible liberation of free formaldehyd, to which the efficiency of the drug is usually ascribed, would seem to make it an ideal drug in infections, and great claims have been made for its efficacy. But the question arises: Is formaldehyd liberated, and if so, is it in sufficient amount to have an antiseptic action?

Hexamethylenamin is readily decomposed into formaldehyd and ammonia in acid solutions, less readily in neutral or slightly alkaline solutions, and not at all in a stronger alkaline medium. When injected intravenously it produces a temporary increase in the rate and depth of respiration which would indicate an ammonium action and a consequent formaldehyd liberation. In addition, formaldehyd is always found in acid urines after administration of the drug. These results might mean a liberation of formaldehyd in all parts of the body; but Hanzlik and Collins[2] and others have failed to find such a liberation in any of the body fluids except the gastric juice and urine. There is a possibility, however, that it is liberated and yet not detected, since one of us (McGuigan) has shown that small amounts of formaldehyd are oxidized in the blood so rapidly that it quickly escapes detection by the ordinary means, even that introduced into the stomach or liberated from hexamethylenamin by the gastric juice and subsequently absorbed. To meet this objection a new method is offered for the detection of free formaldehyd in the blood. This consists in dialyzing the normal circulating blood in animals through collodion tubes interposed between the carotid

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* From the Laboratory of Pharmacology of the Northwestern University Medical School.

* Submitted for publication Dec. 29, 1913.

[1] McGuigan, Hugh: Jour. Biol. Chem., 1912, xi, 33, proceedings.

[2] Hanzlik, Paul J., and Collins, R. J.: Hexamethylenamin: The Liberation of Formaldehyd and the Antiseptic Efficiency Under Different Chemical and Biological Conditions, THE ARCHIVES INT. MED., 1913, xii, 578. This gives a complete review of the literature.

artery and the external jugular vein.[3] The tubes are immersed in water or saline solution and the living blood is dialyzed during the action of the drug. If any formaldehyd is formed, part of it will rapidly pass into the dialysate, where it can be identified by the usual tests. The results show uniformly that hexamethylenamin is found in the dialysate in a few minutes after the injection, while free formaldehyd is not detected even after several hours of dialysis. The following protocol will illustrate:

Male dog. Ten kg. Ether anesthesia.

1: Collodion dialyzing tubes attached to the carotid artery and external jugular vein.

1:20: Dialysis commenced. Tests of the dialysate for hexamethylenamin and formaldehyd negative. 100 c.c. of 3 per cent. hexamethylenamin in 0.9 sodium chlorid slowly injected into the femoral vein in the next ten minutes.

1:40: Dialysate tests: Hexamethylenamin positive; formaldehyd negative.

2: Dialysate tests: Hexamethylenamin positive; formaldehyd negative.

4:10: Dialysate tests: Hexamethylenamin positive; formaldehyd negative. Urine strongly positive to free formaldehyd tests.

4:30: During the next ten minutes 40 c.c. 0.5 per cent. formaldehyd injected slowly into the femoral vein.

4:40: Dialysate test shows free formaldehyd.

In control experiments the injection of formaldehyd only always gave free formaldehyd in the dialysate. Some hexamethylenamin is also formed. The Jorrisen and Rimini tests were used for free formaldehyd, and Hehner's test for the combined form.

It is evident that formaldehyd is not liberated in amounts sufficient for detection with the phloroglucin or phenylhydrazin tests. Since these reagents will detect amounts far less than enough to have any antiseptic action, hexamethylenamin antisepsis, if any, cannot be due to decomposition products. But even though formaldehyd were liberated in minute amounts it would not have the reputed hexamethylenamin effect, since after injection small amounts of free formaldehyd are so rapidly oxidized that antiseptic action is improbable, while in larger amounts it is decidedly injurious.

Hexamethylenamin itself has no antiseptic action on yeast or bacteria outside of the body, but the possibility still remains that the mere entrance and exit of the drug may have a beneficial action when taken internally.

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[3] Abel, John J., Rowntree, Leonard G., and Turner, B. B.: Removal of Diffusible Substances from the Circulating Blood of Living Animals by Dialysis, Jour. Pharmacol. and Exper. Therap., 1914, v, 275. This gives Abel's method without a coagulant. We were unaware of the priority of Abel in this field when the work was done.

SUMMARY

Since, after the administration of hexamethylenamin, free formaldehyd appears only in the gastric juice and acid urine, and not in other secretions or in the blood, even with dialyzing tests, the liberation results from the acid reaction only and not from cell action. Even if it were liberated in other locations it would probably exert no beneficial action because of its reconversion or rapid oxidation into injurious products. Combined formaldehyd as hexamethylenamin, does not decompose readily until an acid medium is reached, when the action is that of weak formaldehyd. The only apparent indication for the internal administration of the drug, therefore, is in infections of the urinary tract.

SOME RELATIONS OF THE BRAIN AND OF THE OLFACTORY APPARATUS TO THE PROCESSES OF IMMUNITY *

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The body is provided with three obvious lines of defense against infection, namely, its peripheral epithelium, its blood and lymph, and its tissue cells. The activity of modern investigators has been engrossed almost wholly with study of the last two; the first has received very little attention. Yet it is indisputable that the epithelial covering of the body must have intrinsic resources of protection against adverse influences which are in such habitual action that its relations should be considered truly physiological, rather than pathological, as its response to adventitious agencies would be. In short, a study of the pathologic physiology of the peripheral epithelium must conceive of it primarily as a mechanism for the *prevention* of disease rather than, as in the case of the body-fluids and tissues, an establishment for producing the means of *cure*. While the protoplasm of the surface cells must be endowed with a degree of autonomy involving capacity for independent response to irritation, which possibly includes the production of specific antibodies, its striking peculiarity is its abundant supply of sensory nerves, largely endowed with "specific energy," through which every external stimulus is made to provoke an immediate and universal internal response.

The incitement to the investigation the report of which follows was a desire to develop the existence of some immunological relations between the peripheral and the central mechanisms. If *a priori* conceptions are given undue prominence at the outset, a measure of defense may be found in the wise dictum of Richet,[1] that in biologic research the guiding thread must always start from the teleologic point of view.

Modern therapeutics offers abundant illustration of the beneficent influence of physical agencies acting externally. The criterion for the usefulness of cold water in the treatment of typhoid fever is the "physiological response" which its application may provoke. As Chantemesse points out, the hydriatric stimulus probably does not excite the formation of specific antibodies against the invading noxa, but it seems probable that the *capacity* for the formation of antibodies is enhanced indi-

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* Submitted for publication Dec. 17, 1913.

[1] Richet, Charles: Ann. de l'Inst. Pasteur, 1907, xxi, 497.

rectly, through reflex excitement of the various motor and metabolic mechanisms. Similarly, the benefits of the open-air treatment in tuberculosis are in some way due to physiological response to external agents, which, as in another place I have attempted to show, exert their influence largely through the temperature nerves of the skin. There is good reason to believe that at least the vital capacity for the formation of antibodies is largely under the control of external stimuli which make up the environment of what is known as the "hygienic life." The fact that tuberculosis finds least resistance to its development in the tissues of those who, like the American Indians, from a habitual open-air life are suddenly forced to conform to the restraints of civilization, argues that hygienic living produces no specific antibodies against this disease.

But there is abundant clinical evidence that a great variety of antigens can produce specific anaphylactic systemic response when applied to the peripheral epithelium. The assumption that such antigens must be absorbed into the circulation before becoming effective, while probably correct in general, is unwarranted without direct evidence. The urticarias and other anaphylactic phenomena following the ingestion of certain articles of food by some people, and, especially, the asthmatic paroxysms induced by the inhalation of certain odors, belong to one of the most interesting divisions of clinical pathology. Indeed, it was an incident related to me by V. C. Vaughan, Jr., of Detroit, which gave the final impulse to the present investigation.

Vaughan's account is as follows: The patient was a man, aged 36, who was suffering from moderately advanced tuberculous disease of the lungs complicated by recurrent hemoptyses. From March 11 to 13, inclusive, the patient received three injections of fresh, normal rabbit's serum of 0.1 c.c., 9 c.c. and 10 c.c. April 7, twenty-seven days after the first injection, a rabbit was brought into the patient's room, was handled by him and allowed to run about the bed. Between three and five hours after this event the patient suffered an asthma-like attack — the first which he had ever experienced.

As indicated at the outset, my conception in the main has been that phenomena which are essentially anaphylactic form a conspicuous feature of normal sensory activity. The mysterious ability of the hound to follow a definite trail unconfused by a multitude of other footsteps is cleared up at once if we assume that the dog's olfactory apparatus is sensitized to the odor which he follows. One is tempted to suggest that even the phenomena of complementary color sensation, as manifested in the "after-images," are but the psychic signs of specific antibodies formed in the retina.

The experiments to be described were performed on guinea-pigs. Sensitization was achieved by subcutaneous injection of normal horse-serum obtained from a commercial source. The sensitizing dose usually varied from 0.25 to 0.5 c.c. The toxic injection was invariably given through the jugular vein. Many intracranial operations were performed, including cutting the olfactory nerves or ablation of the olfactory lobes alone or with a certain bulk of the anterior cerebrum. Anatomically the guinea-pig is excellently adapted for such work. As is well known, the anatomical relations of the sense-organ for smell are almost unique.[2] It is constructed peripherally of nerve-cells inclosed within the olfactory mucous membrane. Processes directed distally from the nerve-cells project freely like bristles from the free surface of the membrane, while from the opposite poles "teledendrons" find their way into the cranial cavity to embrace the nerve-cells of the olfactory lobes.

This research would have been quite impossible but for the devoted aid given by my colleague, Dr. Cuthbert Powell, who has freely lent his surgical skill to the performance of the many scores of surgical operations involved in the investigation.

GUINEA-PIGS SENSITIZED TO HORSE-SERUM MAY BE DESENSITIZED BY SOJOURN IN A HORSE STABLE

The first effort made was to elicit some sign of anaphylaxis in the peripheral epithelium of a serum-sensitized animal. A guinea-pig, which had received a subcutaneous injection of horse-serum thirty-eight days before, was held gently on its back and horse-serum in droplets was allowed to fall into each nostril. I expected to witness some sign of specific irritation. The result, however, was wholly negative. The animal a few hours later received an intravenous injection of 0.5 c.c. of horse-serum and died in about three minutes with characteristic symptoms. Another sensitized pig was made to inhale finely vaporized serum, in the manner to be described later, but, as in the first case, the results were negative. These observations were repeated on numerous occasions with different animals and the results all pointed to the conclusion that *guinea-pigs sensitized by subcutaneous injections of horse-serum manifest no particular irritation when the same serum is instilled into the nose or given by inhalation.*

It then occurred to me that possibly the aroma of the animal producing the sensitizing antigen might develop some characteristic reaction. Accordingly, four guinea-pigs were placed in a box covered with wire netting. Two of the animals were normal and two, forty days previously, had each received subcutaneously from 0.5 to 0.75 c.c. of serum. The box was carried, July 7, to a livery stable in which a score or more of horses were maintained. The air of the stable at this time was powerfully impregnated with a characteristic odor and there was a particularly pungent quality to the smell. Later in the season, as cooler weather advanced, the intensity of the odor diminished and its pungent quality disappeared. There was, as will be seen directly, a coincident change in the biological reactions. The box had been in the stable possibly five minutes when marked nervous disturbances were manifested by the two sensitized animals. One of them, a female weighing 480 gm., showed marked excitement, dashing about the box and biting at her companions, then scratching the nose vigorously. These symptoms subsided in about half an hour. The other sensitized pig, weight 195 gm., lay prone or squatted on the floor of the box and emitted plaintive sounds. The animals were kept in the stable overnight and appeared wholly normal when removed next morning. The control animals showed no particular disturbance.

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[2] Troland: Am. Jour. Physiol., 1913, xxxii, 19.

Some drops of serum were instilled into the nostrils of the smaller sensitized pig and provoked within a few moments somewhat the same reactions as the animal had manifested in the stable. This experiment was, under these conditions, unfortunately not repeated. More than twenty-four hours after its introduction into the stable and about eight hours after its removal therefrom, the larger sensitized pig was given by the vein nearly 1 c.c. of horse-serum. *There was no marked reaction;* soon after its release from the holder the animal fed as usual. Twenty-five days later this pig received another intravenous injection of serum and died within four minutes. The smaller of the two sensitized pigs received its toxic dose some twenty-eight hours after removal from the stable. Owing to difficulties in manipulation a great excess of serum was injected into the vein, probably more than 1 c.c. The animal did not suffer the usual shock, but died from respiratory failure in about half an hour; its lungs were almost completely collapsed when the chest was opened.

In the light of later observations I am inclined to think that this animal's death was a sign of the passing of the phase of antianaphylaxis induced by inhalation of stable-air combined with the excessive magnitude of the toxic injection. No effort was spared, of course, in seeking a solution of the results obtained in these preliminary experiments. Of fundamental importance appeared to be the question whether the desensitizing agent in the air of the stable affected the body indirectly through action on the olfactory mucous membrane or was absorbed directly through the respiratory tract. To resolve this question, groups of pigs, sensitized or normal, were operated on for section of the olfactory nerves. Under ether, a small hole was trephined just posterior to the cribriform plate, the nerves were cut with a fine bistoury and their stumps wiped out with a small pledget of cotton held in forceps. The animal manifests little or no disturbance after such an operation.

In other animals not only the olfactory nerves were removed but the olfactory lobes as well. But, for reasons that will be detailed later, this more extensive operation was necessarily performed only on normal, non-sensitized animals. The experimental data are condensed in the following protocols:

Experiment 1.—Four sensitized guinea-pigs, two with intact olfactories, exposed to stable August 18.

Pig 1, male, 480 gm.; olfactory nerves excised July 12; sensitized with serum July 16. No reaction in stable.

Pig 2, male, 645 gm.; sensitized July 16; olfactory nerves excised August 15. Restlessness after twenty minutes in stable.

Pig 3, male, 675 gm.; unoperated, sensitized July 16. Much erotic excitement after fifteen minutes in stable.

Pig 4, male, 750 gm.; unoperated, sensitized July 16. No reaction except slight uneasiness after forty minutes in the stable.

After remaining all night in the stable each animal received, August 19, an intravenous injection of more than 0.5 c.c. of fresh serum. Every pig died in characteristic shock except Pig 3, which responded to the injection with violent struggles, some respiratory râles, deepened respiration and rubbing of the nose when released. After this moderate shock the pig completely recovered.

One cannot fail to connect the excitement of this pig when exposed to the stable air, attempting to copulate with his male companion, etc., with the desensitization certified by the development of antianaphylaxis. This animal was reexposed in the stable thirty-three days later, when he showed but slight excitement, and the following day he succumbed to intravenous injection.

Experiment 2.—Two pigs received subcutaneous serum July 16. Exposed in stable August 20.

Pig 1, male, 525 gm. Olfactories intact. Within five minutes after entering stable is erotic and continues restless, scratches nose, etc., for an hour.

Pig 2, male, 540 gm. Olfactory nerves had been cut July 12, and a serum inhalation given August 16. In the stable is restless, slightly dyspneic and scratches chin during an hour.

August 21, intravenous injection of serum, more than 0.5 c.c., was given to each. Pig 1 had two slight spasms, sneezed twice and then recovered. Pig 2 showed very little reaction. Result, antianaphylaxis in both animals.

The recovery of the second animal would appear to show that the olfactory apparatus was not concerned in the desensitization, but on August 22, its brain was exposed for the purpose of excising the olfactory lobes; it was then found that the olfactory nerves appeared to have regenerated in the interval of thirty-nine days elapsing between the nerve section and the stable exposure.

EXPERIMENT 3.—Two pigs sensitized July 16. Both had been in the same box with the animals used in a former experiment. They were placed again in the stable for forty minutes, August 22. Twenty hours later they received the toxic injection.

Pig 1, male, 660 gm. Somewhat erotic and restless in stable.

Pig 2, male, 360 gm. Olfactory nerves cut July 12. Restless and rubs nose in stable.

Both died from the toxic injection, which, it will be noted, was given twenty hours after leaving the stable, whereas the usual interval was two or three hours. Necropsy on Pig 2 indicated partial regeneration of the olfactory nerves.

EXPERIMENT 4.—Two pigs sensitized July 16. Placed in stable for five hours, August 25.

Pig 1, 425 gm.; a comparatively feeble animal. Restless, rubs nose and scratches in the stable.

Pig 2, 790 gm.; olfactory nerves were cut, August 24. Less excitement shown in the stable than in the case of Pig 1.

Intravenous injections of more than 0.5 c.c. of serum were given within an hour of removal from the stable. Pig 2 died promptly from shock. Pig 1 showed no reaction except for temporary muscular weakness becoming apparent in an hour. This animal was undoubtedly antianaphylactic but was found dying the next morning after exposure to the cold of the previous night. It was frequently noted that guinea-pigs recovering from the strain of anaphylactic shock are exceedingly non-resistant to external cold. Their temperature regulation is apparently profoundly disturbed.[3]

It is unnecessary to go further into detail along this line of evidence. Suffice it to say that a large proportion of guinea-pigs sensitized subcutaneously to horse-serum were desensitized by exposure to the air of the horse-stable. There was a very obvious relation between the pungency of the stable-odor and the latent period of anaphylactic disturbance. When the smell was most intense the nervous symptoms of anaphylaxis came on almost immediately. In Denver the nights became strikingly cool in August so that the more intense stable-odor only endured for two or three weeks in July and the time required to sensitize guinea-pigs did not allow of prolonged investigation under conditions most favorable to olfactory stimulation.

As the mean temperature of the air fell and the stable odor became less intense the latent period of anaphylactic disturbance increased from a very few minutes to a quarter of an hour, then to longer periods and finally the onset of disturbance could not be distinguished. Nevertheless sensitized pigs kept in the stable for a day or more sometimes proved to be antianaphylactic to intravenous injection even when they had manifested no striking symptoms marking desensitization.

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[3] Doerr: In Kolle and Wassermann's Handbuch des pathogenen Mikroorganismen. 1913, ii, Part 2, p. 1070.

All the earlier observations pointed to the conclusion that only pigs possessing intact olfactory mechanisms were subject to desensitization through the stable air. Obviously a single positive result demonstrating antianaphylaxis in the case of a smell-free guinea-pig would show that the noxa producing desensitization could affect the body through channels other than the olfactory. Such a demonstration was afforded by observations on four animals kept in the stable for three days during the first week in October. Each had suffered either recent section of its olfactory nerves or loss of both olfactory nerves and lobes many weeks previously. Submitted to the test of intravenous inoculation, one of the pigs whose olfactory lobes had been excised thirty-nine days before and which had been sensitized by subcutaneous serum thirty-six days before, recovered from the toxic injection after slight symptoms of shock.

This section of my work may be briefly summarized by stating that fourteen sensitized guinea-pigs with intact olfactory sense were exposed to the stable air. Of these, five became completely antianaphylactic to the intravenous toxic injection and two succumbed only after evidence of great resistance to the toxic dose. The fourteen pigs included two that had been previously made antianaphylactic as witnessed by recovery from an intravenous injection; both died from the second intravenous dose. The fourteen pigs also included two in which the olfactory nerves had been cut long before but which seemed to have regenerated.

Ten sensitized pigs were exposed in the stable after recent section of their olfactory nerves or long-standing ablation of the olfactory lobes. None of these had manifested any marked symptoms of anaphylactic disturbance in the stable. Only one of this group survived the toxic intravenous injection.

Daily contact with such phenomena as have been described is bound to give rise to certain more or less defensible impressions which have not been submitted to definite proof. Of this nature are the notions that the desensitizing agent in the stable-air operates on the body in two ways: (1) acutely, as an odor irritating the olfactory nerves with the production of anaphylactic symptoms; (2) more slowly, by absorption through the respiratory tract, without the production of striking anaphylactic symptoms. The important question as to whether antianaphylaxis can be produced by the mere odorous stimulation of the olfactory epithelium has not been settled, although the facts seem to point in that direction. The phase of antianaphylaxis in these experiments, as found in other fields, comes on very soon after exposure to the exciting cause. Also, several experiments pointed to the conclusion that the antianaphylactic period is very short — that it is rapidly vanishing within twenty-four hours after removal from the desensitizing environment.

The theory having been proved that fully developed sensitization could be temporarily undone by exposure of animals to stable air, the conclusion seemed obvious that sensitization should be altogether prevented in pigs kept in the stable during the latent period of sensitization. The result of an appropriate experiment proved, however, directly the contrary, as follows:

Experiment 4.—Five guinea-pigs, weighing about 350 gm. each, were placed in the stable October 24, about twenty hours after receiving subcutaneous injections of serum, with the exception of one animal which had received an injection ten days before. This last pig was taken from the stable October 29, that is, fifteen days after its sensitizing injection and at the end of five days' residence in the stable. An intravenous injection given at this time was fatal within four minutes. The remaining four pigs were taken from the stable November 17, after exposure of fourteen days, and each succumbed to an intravenous injection within about three minutes. Necropsy was performed on these, as in all other fatal cases, and the lungs were found in characteristic anaphylactic distention. Guinea-pigs of this group manifested a somewhat striking difference in behavior from all other animals exposed in the stable. They never recovered from the timidity associated with the change of environment, nor did they acquire a normal appetite for food. The results of the experiment indicate that, at least in cool weather, the processes leading to sensitization go on in the environment which may effect desensitization of a fully sensitized animal.

SENSITIZATION TO HORSE-SERUM IS NOT CAUSED BY EXPOSURE TO STABLE AIR

As to the nature of the agent producing the desensitizing effects, I have no definite evidence. When the box containing the guinea-pigs was held directly under the nose of a horse, or when the manure-impregnated straw of the stable was placed within it no particular reaction was observed. An effort was made, of course, to sensitize the guinea-pigs to horse-serum by the same influence which caused their desensitization.

The two normal pigs which had been used as controls and exposed to stable air, July 7, each received an intravenous injection of 0.5 c.c. of horse-serum sixty-three days later. There was nothing like shock to be discerned, though one of the animals rubbed its nose vigorously ten minutes after its release, the other seemed sleepy and both preened the body as if stimulated by itching.

Four normal male pigs, weighing about 390 gm. each, were placed in the stable, September 9. One of them was removed after twenty-four hours and within an hour thereafter received an intravenous injection. There was no reaction except that the animal remained rather unusually quiet. For fourteen days the remaining pigs were kept in the stable, two of them being taken out for some hours each day. One of these and the third pig — which had been continuously in the stable — were given intravenous injections within about an hour after removal, with completely negative results. The evidence shows that while the possibility of minor degrees of sensitization to toxic injections of serum cannot be denied, nothing like the sensibility leading to fatal shock is induced.[4] The slighter degrees of anaphylactic reaction are somewhat uncertain in significance since the normal pig is prone to manifest the same actions, such as nose-rubbing and preening the body.

ANAPHYLACTIC SHOCK AND DESENSITIZATION CAUSED BY OPERATIONS ON THE BRAIN OF THE SENSITIZED GUINEA-PIG

According to the well-known views of Besredka,[5] sensitization in the guinea-pig is primarily or wholly a property of the brain. This author holds the view that during the process of sensitization the body tissues form a substance *une sensibilisine,* which fixes itself to the brain-cells. Intracerebral injection of a large dose of serum (0.25 c.c.) produces rapid desensitization with great shock or death. With small intracerebral injections (0.0025 c.c. to 0.025 c.c.), desensitization of the cerebrum comes gradually and the animal becomes antianaphylactic. The animal is resensitized by a new injection made within this period. He holds that the condition of antianaphylaxis is a return to the normal state. Guinea-pigs may be desensitized by intracerebral injections but cannot be sensitized thereby, that is, the brain-cells cannot prepare the sensitizing substance. In an animal thoroughly narcotized by ether, the intracerebral injection of serum produces no shock but still induces antianaphylaxis.

That brain sensitization cannot altogether account for the phenomena of anaphylactic shock was sufficiently demonstrated by Auer and Lewis,[6] who found that sensitized guinea-pigs were killed by intravenous injection and showed characteristic distention of the lungs after section of the vagi nerves and after destruction of the base of the brain, medulla and spinal cord. That the irritability of the brain is profoundly modified by the state of sensitization was early made clear in our experiments.

In attempting to remove the olfactory sense from sensitized pigs in preparation for the stable experiments, it was found that while intracranial section of the olfactory nerves produced no particular reaction, ablation of the olfactory lobes caused profound disturbance, as illustrated in the following experiment:

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[4] Not until this work had been long completed did I learn that Rosenau, in an announcement I have not been able to trace, describes successful efforts to sensitize guinea-pigs in a horse stable.

[5] Besredka, A., and Steinhardt, E.: Ann. de l'Inst. Pasteur, 1907, xxi, 117; Besredka, A.: Ann. de l'Inst. Pasteur, 1907, xxi, 777 and 950; ibid., 1910, xxiv, 273, 879, etc.

[6] Auer and Lewis: Jour. Exper. Med., 1910, xii, 151.

Experiment 5.—Four guinea-pigs, about 730 gm. each, were given subcutaneous injections of 0.33 c.c. of serum, July 16. August 15, under light ether anesthesia, the olfactory nerves were cut and wiped out in three animals; there was no special reaction. In the fourth pig, which received the least ether, both olfactory lobes and nerves were removed. After its release the animal continued to lie on its side and in about fifteen minutes severe clonic convulsions of the limbs appeared, lasting half an hour or more. The animal gradually recovered, but more than two hours after the operation manifested rhythmic "bucking" movements of the body without the feet leaving the floor. Next day this animal was well and was given 0.75 c.c. of serum intravenously; there was no reaction except for slight torpor. One of the first three pigs was given a like injection immediately afterward and died within three minutes.

It should be said that removal of the olfactory lobes in a normal guinea-pig produces no definite response. The shock and subsequent antianaphylaxis described are no special effect of removal of the olfactory lobes, but follow mutilations of the cerebrum, thus:

Experiment 6.—A vigorous male pig, 700 gm., was sensitized July 16. August 23, under ether, an amount of cerebral tissue in bulk about that of the olfactory lobes was removed from the parietal regions. The animal when released continued for ten minutes to lie on its side with clonic twitching of the hind legs. The next day this pig received an intravenous injection of 0.75 c.c. of serum and, with the exception of slight asthmatic wheezing, showed no special reaction.

Experiment 7.—Male pig, 780 gm., sensitized August 14. August 21, a bulk of cerebrum in size five or six times that of the olfactory lobes, was removed. For nearly an hour the pig lay on its side with clonic twitchings, increasing to convulsions, of the legs. It sprang up and bucked after sitting up and then for many hours carried on continuous coordinated forced movements, seeking always to escape restraint and wander forward. The next morning the animal was found dead. The fatal result was probably brought about partly by failure to react to the lowered temperature of the night air.

Numerous experiments of like character have definitely proved that anaphylactic shock is caused by mutilation of the brain in the sensitized guinea-pig. The degree of shock seems rather strictly related to the amount of cerebral tissue removed, but varies somewhat in different animals. The intensity of shock suffered after a definite nerve injury seemed to diminish as the weather became cooler. If this impression is confirmed it may be elucidated by the facts portrayed in the next section of this paper. In the accounts[7] of anaphylactic shock and the resulting phase of antianaphylaxis usually given, the phenomena have been induced by reinjection of the antigen which caused sensitization, but here are examples of profound somatic changes being induced by mere ablation of brain-tissue in amounts whose loss would cause no particular disturbance in a normal animal. In seeking an explanation

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7. Doerr: In Kolle and Wassermann's Handbuch der pathogenen Mikroorganismen, 1913, ii, Part 2, p. 1085.

for the facts it seemed probable that the effective stimulus consisted in the mechanical agitation of the brain. To test this view an electric vibrator, designed for therapeutic massage, was used, its flat ebonite disk, rapidly oscillating, being firmly applied for three minutes to the skulls of a series of sensitized guinea-pigs which were slightly etherized. The results showed a curious discrepancy.

Experiment 8.—A guinea-pig previously described, which had received a subcutaneous injection of serum July 16, had lost part of its cerebrum August 23, and had recovered from an intravenous injection August 24, was submitted to skull vibrations September 22. The only reaction to the vibration was rubbing of the nose and a slight "steppage" movement. September 23 more than 0.5 c.c. of serum was given intravenously, resulting in dyspnea, peristalsis and cough, but recovery within an hour. (This animal received another vibration November 9, followed by intravenous injection November 11, from which it recovered. Another intravenous injection was given fourteen days later with recovery, and a fifth injection into a vein was made December 9, without producing symptoms. This is a case of either prolonged antianaphylaxis or permanent immunity.)

Experiment 9.—Guinea-pig, male, 820 gm., sensitized July 16. From August 16 to August 31 it received five inhalations of vapor of horse-serum without effect. September 2 the electric vibrator was applied to its skull for about five minutes. There was no reaction except "steppage" movements, nose rubbing and slight incoordination. The next day the animal received intravenously 0.75 c.c. of serum and fully recovered with very slight symptoms. (Twenty days later the olfactory lobes were removed. The shock was very intense. The animal never fully recovered, though it would eat greedily; it died four days after the operation.)

The results of subsequent experiments indicate that desensitization caused in the foregoing animals by vibration of the skull was dependent in some way on the treatment they had previously received auxilliary to the primary sensitization. Five other guinea-pigs, two of which had been sensitized intravenously, were submitted to vibration and all died in shock when injected the following day by the vein. Two of the animals before the toxic injections received no less than six vibration-treatments at intervals of two days. The application of the vibrator to the skull is exceedingly drastic treatment and frequently resulted in complete inhibition of the respiration and great slowing and enfeeblement of the heart-beat.

The phase of antianaphylaxis produced by the shock of brain operations is very short. It passes off in less than forty-eight hours, as was evidenced by three special experiments which it is not necessary to detail. That no shock is occasioned by moderate ablation of nervous tissue in the normal pig is shown by the following:

Experiment 10.—Normal male, 360 gm. Olfactory lobes and a portion of the anterior cerebrum slightly greater in bulk were removed November 3. There was no reaction whatever. (In two days this pig sickened, probably from infection, and died in a week. Other normal pigs suffered loss of much greater quantity of brain without permanent disturbance).

In a widely quoted paper, Schürer and Strasmann[8] describe experiments in which they attempt to contravert Besredka's idea that the sole seat of the anaphylactic reaction is in the brain. They excised the whole brain, including the basal ganglia, in sensitized guinea-pigs and then gave them serum by intravenous injection. The animals died within a period varying from a few minutes to several hours, and the results were supposed to contravert the theory that the brain is involved in anaphylactic phenomena. In the light of my observations it is plain that such methods are necessarily incompetent to clear up the subject.

DESENSITIZATION OF THE BRAIN THROUGH SECTION OF THE OLFACTORY NERVES

On one occasion, the olfactory lobes were removed from a fully sensitized guinea-pig but the animal manifested no sign of shock whatever. In seeking the cause for this departure from the rule that had seemed established, it was found that this pig had, eight days before, been subjected to section of its olfactory nerves. It at once became necessary to follow out the suggestion aroused by this development.

Experiment 11.—Six young pigs, weighing about 270 gm. each, were sensitized by subcutaneous injection August 29. From four of these, Pigs 1, 2, 3 and 4, the olfactory nerves were cut and wiped out September 16, under very slight etherization. There was no reaction except to a very slight degree in one (Pig 2) in which bleeding occurred through the nose due to injury to the cribriform plate. September 24, twenty-six days after subcutaneous injection, the olfactory lobes were removed from Pigs 1, 2 and 5 (the latter having intact olfactory nerves). Pigs 1 and 2 showed no shock; Pig 5 lay on its side for nearly ten minutes with somewhat convulsive clonic trembling of the legs. This shock did not produce antianaphylaxis for the animal succumbed to intravenous injection the next day. September 25 the olfactory lobes were excised from Pig 3. There was no shock whatever, the animal sitting up at once when released, though it rubbed its nose and preened the body. On the same date there were taken from Pig 4 (olfactory nerves destroyed September 16), both the olfactory lobes and a portion of the anterior cerebrum, about equal in bulk to the combined olfactory lobes. The animal lay quietly on its side for two minutes after release from the holder, breathing hard but without convulsive movements, and then sat up with normal appearance except for slight temporary spasmodic nodding of the head. No antianaphylaxis was produced, for the animal succumbed to an intravenous injection the next day, September 25. Pig 6, sensitized but with intact olfactory nerves, was made to lose its olfactory lobes and a portion of the anterior cerebrum equal to a single olfactory lobe. When released this animal lay on its side for five minutes with clonic convulsions. It then sat up and appeared normal for awhile, but soon became restless and the subject of forced movements, which continued until the animal died in convulsions, attended with enormous erections of the penis, after six hours. At necropsy the lungs were found collapsed, containing a few hemorrhagic areas but no consolidation.

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[8] Schürer, J., and Strasmann, R.: Ztschr. f. Immunitätsforsch., 1912, xii, 143.

The experiments show very definitely that in sensitized guinea-pigs the nervous shock following mutilation of the brain is greatly reduced eight or ten days after section of the olfactory nerves. It was sought to determine how soon such desensitization of the brain followed on nerve section, and how long it continued.

Experiment 12.—Pig 1, male, 440 gm., sensitized August 29. Olfactory nerves destroyed September 24. Next day the olfactory lobes were removed. The animal manifested moderate but decided action, such as relatively slow recovery from the operation followed by nose-rubbing and clonic tremblings of the body. The shock was not sufficient to produce antianaphylaxis for the pig succumbed in three minutes next day to toxic injection.

Pig 2, female, 910 gm., far advanced in pregnancy, sensitized August 29. Olfactory nerves cut November 5. November 6 the olfactory lobes and a like bulk of cerebrum were removed. There was scarcely any shock following the operation, the only sign of anaphylaxis being a slight inspiratory humping of the body setting in ten minutes after release.

These results indicate that while the desensitizing effect of olfactory nerve section on the brain may develop within a day, the full influence of the deprivation of olfactory stimuli is not established with certainty till later.

Experiment 13.—Male pig, 500 gm., sensitized August 29. Olfactory nerves cut November 5. November 18 excised olfactory lobes and a similar bulk of cerebrum. The animal lay quiet for nearly ten minutes after release and then sat up with no evidence of reaction except for slight rhythmic lifting of the legs. Next day the pig succumbed in three minutes to the toxic injection.

It is clear from these experiments that the diminished sensibility of the brain following section of the olfactory nerves in sensitized guinea-pigs may be well marked within twenty-four hours and remains in full force for at least thirteen days. After longer periods there may always be suspicion of regeneration of the olfactory nerves. In the following experiments part of the cerebrum was removed long after ablation of the olfactory lobes:

Experiment 14.—Female pig, 690 gm. Olfactory lobes removed August 27 and the space left filled with melted paraffin (in none of several cases in which this was done could the paraffin be detected with certainty after several weeks). Serum was injected subcutaneously August 29. November 3, sixty-eight days after removal of the lobes, under slight ether anesthesia, there was scooped from the anterior cerebrum an amount of tissue estimated as about twice the bulk of the normal olfactory lobes. There resulted moderate but distinct shock, with some forced movements, which passed off after about thirty minutes. Two days later the animal withstood an intravenous injection of nearly 0.5 c.c. of serum with scarcely any reaction.

This experiment indicates that after removal of the olfactory lobes (of course including the attached nerves) the sensitiveness of the brain to laceration has been more or less completely restored in about two months. Similar conclusions were derived from other experiments the conditions of which were more complicated, which it is unnecessary to describe.

It might be claimed that the influence on the irritability of the brain apparently exerted by the olfactory sense is not a specific property of this sense but is wielded by any strong sensory impulse or is also a part of the function of other special senses. I did not fully grasp, until too late to sensitize new animals, the importance of testing the relation of the visual sense to cerebral irritability. A single experiment, however, went to show that the removal of one eye does not desensitize the brain as in the case after section of the olfactory nerves.

EXPERIMENT 15.—Male, 615 gm. Sensitized by intravenous injection of 0.5 c.c. of serum September 6. Under ether anesthesia left eyeball was removed November 6. November 10, under ether, the olfactory lobes and an equal bulk of cerebrum were removed. There was moderate but pronounced shock lasting for more than half an hour. The shock was not sufficient to protect the pig with anti-anaphylaxis when an intravenous injection was given next day.

From the results that have been described in the last two sections of this work it seems impossible to avoid the conclusion that sensitization of the brain and sensitization of the body represent different biologic conditions. The former is a labile, the latter a stabile, state. The threshold of irritability of the sensitized brain is plainly leveled in response to olfactory sensory stimuli. The brain may be completely desensitized without affecting in the least the response of the body to the second, toxic dose of the antigen. An attempt to elucidate the teleological significance of these coordinations will be made in the discussion at the end of this paper. As is well known, Besredka asserts that the intracerebral injection of 0.25 c.c. of serum will, in an unanesthetized sensitized guinea-pig, cause speedy anaphylactic death. If the conclusions drawn above as to desensitization of the brain following section of the olfactory nerves be correct, it should be possible for an animal so treated to resist Besredka's fatal injection. That this is true is proved by the following:

EXPERIMENT 16.—Pig 1, female, 360 gm., sensitized August 29. Olfactory nerves cut and wiped out September 16. September 26, under light ether anesthesia, a trephine hole was made over the cerebrum and there was injected through a hypodermic needle into both hemispheres a total of 0.25 c.c. of horse-serum. The animal was practically out from under the influence of ether during the injection. There was but very slight reaction marked by restlessness and some jerking of the head. This animal weighed 450 gm. November 5, when it received an intravenous injection and died in four minutes.

Pig 2, female, 840 gm., sensitized August 29. Olfactory nerves cut November 5. November 8 the skull was trephined over posterior cerebrum and the animal was released until entirely recovered from ether; then, as before, 0.25 c.c. of serum was injected into the brain. There was rather severe shock marked by clonic twitchings of legs, rapid breathing, circular movements, weakness of hind legs; gradual recovery after an hour or two. This shock was not sufficient to produce antianaphylaxis, for the animal succumbed next day in the usual way to intravenous injection.

Besredka found that intracerebral injections made with very small amounts of serum, or made under deep ether anesthesia, are not lethal, and the following day the animal is found to be antianaphylactic. Rosenau and Anderson[9] repeated these experiments on etherized guinea-pigs and found that seven out of eight animals died from the second injection given next day. These discrepancies may be accounted for by supposing that the duration of the antianaphylactic state may be less as well as more than twenty-four hours.

According to the preceding argument, it should be suspected that ether narcosis affects only the susceptibility of the brain to shock, leaving that of the body unaffected. It was found, in fact, that a sensitized guinea-pig etherized to relaxation, died as quickly from intravenous injection of serum as one treated without an anesthetic. In the earlier experiments of this work the intravenous injections were all given without an anesthetic for fear of masking the anaphylactic symptoms; but in all the confirmatory tests the animals were subjected to a slight etherization, with little or no distortion of reactive symptoms.

Reference was made in the preceding section of this paper to an impression which developed as the result of prolonged experimentation, that the anaphylactic shock caused by the ablation of a definite mass of brain tissue became less intense as the weather turned cooler. Such a result might be expected if the olfactory sense, whose excitation probably varies with the external temperature, be indeed, a physiological regulator of brain irritability.

In his excellent contribution to the great work edited by Kolle and Wassermann, Doerr summarizes his discussion on the site of anaphylaxis thus: "That the real points of attack of the anaphylactic noxa lie in the periphery has been established beyond all doubt."

THE RELATION OF THE OLFACTORY NERVES TO SHOCK IN THE NORMAL BRAIN

The marked dependence of anaphylactic disturbance following operations on the brain of serum-sensitized guinea-pigs on integrity of the olfactory nerves raises the question whether in the normal animal there is not a specific physiological relation between the olfactory sense and irritability of the brain. The literature of cerebral physiology makes it obvious that so profound a problem can only be solved by a great number of guarded observations. Nevertheless, a few experiments were ventured in this field and the results were sufficiently positive to deserve record.

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[9] Rosenau and Anderson: Jour. Med. Research, 1908, xx, 37.

[10] "Das die wesentlichen Angriffstellen der anaphylaktischer Noxa in der Peripherie liegen, ist heute wohl über allen Zweifeln sichergestellt." Doerr in Kolle and Wassermann's Handbuch der pathogenen Mikroorganismen, Ed. 2, ii, Part 2, p. 1078.

Five guinea-pigs were taken which were in very fair condition although they had been inoculated with what was evidently an attenuated strain of tubercle bacilli nearly three months before. In three of the animals the olfactory nerves were cut and two or three days later the olfactory lobes were excised together with a quantity of cerebral tissue estimated at three times the bulk of the lobes. In making this estimate the olfactory lobes were placed on a sheet of paper and three heaps of equal size, scooped from the anterior cerebrum, were laid near by. The operations were performed, as usual, under very light anesthesia. As will be seen, the symptoms of shock were much more pronounced in the two animals whose olfactory nerves remained intact up to the time of the operation.

EXPERIMENT 17.—Pig, 1, weight 600 gm. Excised olfactory nerves November 13. November 15 excised olfactory lobes and about three times their bulk of cerebrum. Pig when released lay for ten minutes apparently conscious, but with clonic tremblings of the legs and slight dyspnea. Recovered quickly; result, very slight reaction.

Pig 2, 485 gm. November 13 olfactory nerves cut. November 16 the olfactory lobes and part of the cerebrum removed as before. The animal lay quietly for six minutes and then sat up without reaction except for some dyspnea, nose-rubbing and rhythmic nodding of the head. Result, very slight reaction.

Pig 3, 510 gm. Olfactory nerves cut November 16. November 18 olfactory lobes and three times their bulk of cerebrum removed. Animal tried to sit up in six minutes after release. There were no convulsive movements, but the animal ran about the room and sought to hide in a dark corner. Normal but dull within an hour. Result, slight reaction as shown by apparently forced movements.

Pig 4, 510 gm. Olfactory nerves intact until time of the main operation November 15, when the olfactory lobes (with nerves) and three times their bulk of cerebral tissue were removed. Pig lay for more than ten minutes after release with clonic tremblings. It then turned on its back with convulsive doubling of the body. It was still unable to sit up in twenty minutes after which there was a convulsive twisting of the body with legs kicking. It soon recovered. Result, marked but moderate reaction.

Pig 5, about 580 gm. Olfactory nerves intact until main operation November 16, when the olfactory lobes and cerebral tissue were excised as before. Pig lay for ten minuntes after release with clonic tremblings of the legs; then there was a tetanoid twisting of the body. Sat up in twenty minutes and manifested apparently forced twisting movements. Within forty minutes the only disturbance was shown by rhythmic lifting of the body. Result, marked but moderate reaction.

In answer to the objection to the use of ether in these experiments it may be said that narcotization was of such light degree that animals in which the olfactory nerves alone were cut would sit up at once without reaction on release from the holder. When nerve-cell tissue was excised the animals lay on the side, with or without convulsive twitchings, for a period apparently proportional to the amount of substance removed; that is, the symptoms were a result of the operation, not of the anesthesia.

INFLUENCE OF COCAINIZATION OF THE NOSE ON THE SHOCK FROM INTRACRANIAL OPERATION

The suggestive surgical conceptions of Crile[11] are recalled by these results and an effort was made to modify the shock of brain operations through an attempt to cocainize the olfactory mucous membrane. It is well known that a solution of cocain sprayed into the nose may completely abolish the sense of smell temporarily. Only a few unconvincing experiments were tried in this direction. A 2 per cent. solution of cocain was dropped into the nostrils of two sensitized guinea-pigs four times in the course of fifteen hours. Then under light ether anesthesia the olfactory lobes and a somewhat greater amount of cerebral tissue were removed from each, with resultant moderate but distinct reaction in each. The shock was much less and cleared up sooner than that which occurred in most sensitized pigs subjected to the same operation without cocain. Each of these animals succumbed next day to intravenous injection. Of four young pigs weighing about 240 gm. each, from a sensitized mother, two were treated with several nasal instillations of cocain. One of these pigs quickly died with symptoms to be detailed later. The other three were subjected to the loss of the olfactory lobes and about three times their bulk of cerebral tissue. There was decidedly less prolonged convulsive reaction in the cocainized pig than in the untreated pigs, though the former showed a high degree of nervous excitement. From the results of observations already detailed it is obvious that cocain anesthesia should be prolonged for a day or two in order to obtain its desensitizing action, if any, on the brain.

CERTAIN ANALOGIES BETWEEN THE EFFECTS OF COCAIN POISONING AND ANAPHYLACTIC SHOCK

Guinea-pigs were killed by nasal instillation of cocain and by subcutaneous and intravenous injection. Five unsensitized pigs were given intravenous injections of cocain in about 4 per cent. solution. Whether the poison was injected slowly or rapidly the result was the same, a speedy diminution in the amplitude of respiratory movement, and death without convulsion. The heart continued beating for many minutes after respiratory arrest just as it does in anaphylactic death. The lungs were found collapsed at necropsy.

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[11] Crile, G. W.: Boston Med. and Surg. Jour., 1910, clxiii, 893.

Three young pigs, offspring of a sensitized mother, weighing 180 to 240 gm. each, were killed by the repeated instillation in the nose of a cocain solution of from 2 to 4 per cent. The symptoms of poisoning came on very suddenly. The animal would fall on its side; the head was tonically retracted; frequent and well-marked opisthotonus and clonic convulsions of legs and body occurred. The same series of events occurred when subcutaneous injections of cocain were given. This was done in the case of seven animals, four of which were serum-sensitized, but the element of respiratory disturbance was more marked than when the poison was given by the nostrils. The retraction of the head was a characteristic symptom, the chest would be distended and the respiratory movements very rapid and so shallow as to be hardly visible. An animal might recover after remaining more than half an hour apparently *in extremis*. The convulsive phenomena witnessed in these animals were exceedingly suggestive of those seen in severe anaphylactic shock. But the particular object of these experiments was to follow out an observation that had been made on the pig from a sensitized mother, which had first succumbed to cocain by the nose. The lungs of this animal were found, post mortem, to be markedly distended, almost as much so as after anaphylactic shock. In two other cases this extraordinary post-mortem distention of the lungs was found, although usually the lungs were well retracted from the heart on the ventral side but maintaining apparently a condition of semi-expansion dorsally. In two normal guinea-pigs killed by cocain subcutaneously the post-mortem lung-distention was less striking than in the sensitized or offspring of sensitized pigs. That the post-mortem distention of the lungs did not depend on the terminal convulsions seemed evidenced by the state of two sensitized pigs which were injected with strychnin; in these the lungs were found completely collapsed at necropsy. The expanded lung after death from cocain offers marked differences from the expanded lung after anaphylactic death. The former is pale, the latter congested. Both remain distended when excised, but the former crepitates little and collapses but slightly when squeezed in the fingers; the latter does both. In that minority of cases in which the lung remains distended after death by cocain, its behavior suggests a rubber-like structure. The phenomena described in this section recall the similar, though still more striking, effects described by Dale and Laidlaw[12] as following the injection into guinea-pigs of betaimidazolylethylamin. They call attention to the anaphylactic-like changes produced by this substance.

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[12] Dale and Laidlaw: Jour. Physiol., 1911, xliii, 182.

REACTIONS OF GUINEA-PIGS TO HORSE-SERUM ADMINISTERED THROUGH THE NOSE AND BY INHALATION IN SPRAYS: LOCAL AND GENERAL ANAPHYLAXIS

Comparatively few investigations seem to have been made with a view to determining the effect of the application of antigens to the unaltered peripheral epithelium. The reaction to the tuberculin test of von Pirquet involves wounding of the outer skin. Administration of antigens by feeding, especially by means of the stomach-tube, greatly complicates the experimental conditions. In an important paper, Dserzgowsky[13] describes experiments in which plugs of cotton wool moistened with the toxin of diphtheria were applied to the mucous membrane of the nose and the toxin itself to the general respiratory tract through the inhalation of sprays. Experiments were performed on horses and on the author himself. It was asserted that in these ways active immunity, both local and general, could be harmlessly induced. Blumenau,[14] following this suggestion, inserted for thirty minutes tampons moistened with diphtheria toxin, diluted to one-third strength, into the nostrils of children. After twenty such treatments diphtheria antitoxin was found in the blood. Practically the same result was obtained by Scheweleff[15] in experiments on dogs. A. C. Klebs,[16] in his history of small-pox inoculation, mentions an ancient custom among the Chinese of protecting against small-pox by putting its virus into the nose.

Busson[17] describes experiments in which guinea-pigs sensitized to horse-serum were inclosed in a tight box and made to inhale a finely divided spray of horse-serum, ten times diluted, for a period of two hours or more. As far as the description can be understood there were very slight but positive signs of anaphylactic reaction. The rise of temperature within the box and the deterioration of the quality of the air must have introduced important complications into the experiment. My results confirm, in general, those of this author.

Schlecht[18] records a series of researches which show that injection of a foreign serum into the body causes in the blood a great temporary increase of eosinophils, and in guinea-pigs of mast-cells as well, due to increased activity of the bone-marrow. The administration of spray inhalations of horse-serum to guinea-pigs, either sensitized or normal, was followed by a high grade of eosinophilia localized in the lungs.

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[13] Dserzgowsky, S. K.: Ztschr f. Immunitätsforsch (abst.), 1910, iii, 602.

[14] Blumenau, N. R.: Ibid., 1910. iv, 353.

[15] Scheweleff, P. P.: Ibid., 1910, x, 1085 (Ref. Bd.)

[16] Klebs, A. C.: Bull. Johns Hopkins Hosp., 1913, xxiv, 69.

[17] Busson, B.: Wien. klin. Wchnschr., 1911, xxiv, 1492.

[18] Schlecht, H.: Kong. f. inn. Med., 1912, xxiv, 416; Deutsch. Arch. f. klin. Med., 1910, xc, 308; ibid., 1912, cviii, 405; Arch. f. exper. Path. u. Pharmakol., 1912, lxvii, 137.

In the discussion of Schleet's paper, read before the Congress for Internal Medicine, Schittenhelm said that he had not been able to repeat the results of Friedberger, who had produced aseptic pneumonia in sensitized guinea-pigs by inhalations of serum.

Ishioka[19] made injections of serum through a fine cannula directly into the trachea of sensitized guinea-pigs. Out of forty animals two died at once in anaphylactic shock; the others showed symptoms but recovered. In a few cases there was produced interstitial pneumonia with much emphysema. In most cases there resulted true lobar pneumonia indicated by patches of infiltration which could even involve a whole lobe.

My method of bringing the serum in contact with the respiratory epithelium differed radically from that described elsewhere. Some two dozen guinea-pigs were treated in two groups; in one the treatment consisted in instilling fresh horse-serum into the nose by dropping it from a hypodermic needle; in the other the serum was breathed as a fine spray. In the first case the animal was gently held by the hand on its back; from an all-glass hypodermic syringe with easily moving piston and a coarse, blunt needle, droplets of serum to the amount of from 0.25 to 0.33 c.c. were allowed to fall into one or the other of the nostrils. As a rule, only one side of the nose was utilized at each sitting. Various animals were treated daily or at intervals of one, two or three days.

The serum spray was produced in a commercial "vaporizer" actuated from a compressed-air tank. The spray thus formed was exceedingly fine and resembled the vapor from a gently boiling teakettle. A funnel made of stiff paper was applied over the nose and mouth of the guinea-pig as it sat on a table. The nozzle of the spray apparatus was closely applied within the smaller but open end of the funnel. The spray was applied at intervals similar to those of the instillations and the sittings lasted, as a rule, about three minutes. The serum was often used in full strength; in dilutions of one-half or one-quarter strength the results appeared the same. Theoretical objections against this method of procedure seem invalid in the light of the reactions obtained.

Each group of guinea-pigs was composed of four subdivisions: (1) normal animals; (2) animals sensitized by the subcutaneous injection of serum; (3) unsensitized animals which had weeks before been relieved of their olfactory lobes; (4) animals which, after the removal of their olfactory lobes, had been subcutaneously sensitized.

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[19] Ishioka, S.: Deutsch. Arch. f. klin. Med., 1912, cvii, 500.

SPECIAL REACTIONS TO THE NASAL INSTILLATION OF SERUM

When horse-serum is slowly dropped as described into a nostril of a guinea-pig for the first time, there is usually no disturbance whatever. The fluid is quickly sucked into the nose, and not until a considerable quantity has been introduced is there any expulsion, and this is evidently mechanical. Late in the sitting, taste and probably swallowing motions are manifested. The nasal canal in a medium-sized guinea-pig has a length of nearly 5 cm. and therefore it is not likely that the first droplets reach the pharynx. Even with the second treatment, after two days, signs of active resistance to the instillation of serum may appear, brisk expiratory sniffing movements more or less resist the entrance of serum or expel it from the nostril.

These minor phenomena are physiologically significant but are difficult to interpret because they may occur with the instillation of normal saline or solutions of cocain at the very first administration. It was noted, however, that active resistance to the instillation of serum appeared uniformly earlier in animals with intact olfactories than in those deprived of their olfactory lobes. In animals treated every alternate day, my notes record signs of great nasal irritation in normal pigs at the second instillation, while in specimens without olfactory lobes it was not until the fourth treatment, after six days, that active reactions were produced.

Previous subcutaneous sensitization had no perceptible influence in accelerating the reactions. One definite and undoubtedly reflex response to the instillation was regularly obtained from certain animals. This was an excess of salivary secretion. While the mouths of practically all pigs which showed signs of irritation against the serum became unusually moist, in a certain number saliva would well up between and drool from the lips. This reaction held constant in the same pigs through a prolonged series of observations. The reaction was usually positive in normal pigs. It was obvious, however, that saliva accumulating in the mouth was frequently removed by swallowing and thus failed to be noted. The reaction can hardly be regarded as other than a sign of specific sensitization. It occurred both in animals previously subcutaneously sensitized and in unsensitized animals, whether with or without olfactory lobes. It did not occur through the instillation of normal salt solution even when it was constantly produced by serum. A single nasal instillation with serum evidently induces sensitization. Thus, October 11, two normal guinea-pigs each received 0.25 c.c. of serum in both nostrils. The only effect witnessed was the excitement of taste movements.

Sixteen days later, October 27, the treatment was repeated. There was now considerable nasal irritation as shown by sniffing and active expulsion of serum from the nose and rubbing of the nose with the paws, and in each case saliva welled from the mouth. Two days later, October 29, one of these animals received an intravenous injection of serum; there was *no reaction.* Five other nasal instillations were given to each pig from November 12 to November 20. The resulting symptoms were the same as those elicited October 27, except that now the animal which had not received the intravenous injection ceased to respond to the instillation by the secretion of saliva. Finally, November 23, both animals received intravenous injections and both died in typical shock. This account anticipates my discussion, but clearly indicates that *local sensitization of the nasal mucous membrane may occur independently of and precede general sensitization.*

The symptoms thus far described as resulting from nasal instillation of serum are minor reactions which it is possible to confuse with those following non-specific stimuli. But there were extraordinary results obtained in the case of a single animal, which, though obviously somewhat dependent on idiosyncrasy, are detailed because they differ only quantitatively from reactions characteristic of this group of experiments. A guinea-pig weighing 435 gm. was treated by the nostrils every second day. During the tenth treatment, eighteen days after the first, the animal suddenly choked; loud rattling râles with occasional cough accompanied the deep and labored respiration. The phenomena strongly suggested those of the severest form of bronchial asthma in man. It was several hours before the pig recovered sufficiently to eat. It had been noticed that spasmodic partial closure of the nostril had resisted the intake of serum. Subsequent administrations of serum each second day provoked similar though milder symptoms, an excessive salivary secretion becoming a relatively more prominent reaction. The symptoms could not have been due to the flow of serum directly into the trachea, for they appeared while still too small a quantity of serum had been applied. Later results with other animals leave no doubt as to the anaphylactic character of the disturbance.

THE EFFECT OF THE INHALATION OF SERUM SPRAYS

The statement was made in the beginning that the initial exhibition of vaporized serum, according to the method described, provoked no symptoms whatever. Guinea-pigs previously sensitized by subcutaneous injection reacted apparently as negatively to the inhalation as did normal animals.

A remarkable difference, however, presented itself in the behavior of those guinea-pigs which received the serum inhalation after a course of serum instillations by the nostril. In these cases there was an immediate response to the first inhalation in the form of a violent dyspnea, with occasional cough, asthmatic in its urgency but characterized by rapid respiratory movement. The attack would develop suddenly within about a minute of beginning inhalation and would not subside for from thirty minutes to several hours. Unfortunately no attempt was made to determine whether a phase of antianaphylaxis succeeded recovery from the attack of dyspnea. Repetitions of inhalation at intervals of two days or more invariably provoked the same response.

Experiment 18.—Two young pigs were treated by instillation of serum in the nose every third and every fourth day from May 28 to July 12. Serum inhalations were given to one July 17, and to the other August 7. Both animals exhibited the reaction described, namely, violent, rapid dyspnea, interrupted with occasional deep breaths and cough.

These, together with subsequent observations, make it clear that local sensitization of the nasal mucous membrane to horse-serum may be induced without the excitement of any very marked reaction. An animal thus peripherally sensitized responds immediately to serum inhalation with characteristic dyspnea, while one sensitized subcutaneously does not. My friend Dr. Hillkowitz kindly tested the blood drawn from the heart of one of the animals described, for precipitins to horse-serum. The dilutions used were 1 : 1,000 and 1 : 10,000. The results were negative, as might have been expected from the similar observations of Rosenau and Anderson.[20] An excellent opportunity seemed presented in these animals to determine whether the olfactory mechanism played any rôle in the serum reactions.

Experiment 19.—A female pig, 645 gm., which had regularly responded to the inhalation, had its olfactory nerves divided August 25. Four days later, and during subsequent exposures, the serum inhalations produced symptoms identical with those produced when the olfactory nerves were intact, though possibly the latent period of reaction was longer. September 2 the olfactory lobes were excised in this pig without special reaction (because of previous section of the nerves). Two days later a serum inhalation provoked the characteristic dyspnea which began after the vaporization of thirty or forty drops of serum. September 10 this animal succumbed, in less than five minutes, to the intravenous injection of 0.5 c.c. of serum.

It was clear in this case, and abundantly confirmed later, that the peripheral application of serum not only sensitized in a peculiar way the peripheral respiratory epithelium but produced general sensitization as well. These results were to have been anticipated from the findings of other observers who used different methods. General body sensitization develops gradually during a course of local treatment with serum and apparently is preceded by the acquisition of local anaphylaxis. An effort was made to trace the development of the reactions of local and general anaphylaxis.

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[20] Rosenau and Anderson: Bull. Hyg. Lab., U. S. P. H. S., 1906, No. 29, p. 35.

Experiment 20.—Two normal male pigs, weighing 360 gm. each, October 11 were made to inhale, with intermissions, for about ten minutes the vapor of a 50 per cent. dilution of serum. There was slight temporary dyspnea, undoubtedly mechanical in origin and due to the long exposure to the vapor (the usual treatment occupied three minutes or less and the specific reaction commonly occurred within a minute or two). October 26, fifteen days later, the pigs having increased in weight, a similar less-prolonged treatment was given. There was no specific reaction, although Pig 1 breathed hard for a while ten minutes later. October 29, three days after the second and eighteen after the first inhalation, Pig 2 received, without ether, 0.5 c.c. of serum intravenously. There was no reaction. November 12 both pigs were again sprayed with serum of 50 per cent. dilution. Almost at once Pig 1, which had not received the intravenous injection, was seized with violent, rapid panting. This passed off in about fifteen minutes. Three days later in the morning this pig was found dead. I cannot account for the fatality except as a result of the treatment combined possibly with low resistance to the cool air of the night. Necropsy showed the olfactory lobes apparently much softened. The lungs were collapsed and congested but without hemorrhagic areas. Pig. 2, which had received intravenous injection October 29, received four serum-inhalations from November 15 to November 20. No dyspnea was caused by either treatment. This animal was given injection of serum by the vein November 23, and died with violent convulsive and bucking seizures.

These observations show that a single inhalation of serum by a normal guinea-pig provokes, when repeated fifteen days later, hardly any perceptible anaphylactic response. A third spraying, performed seventeen days after the last, produces a well-marked reaction. Intravenous injection of serum during these observations may have prevented, it certainly did not exaggerate, the reactions. It was found, as might have been expected, that guinea-pigs treated in precisely the same manner showed more or less individual differences in behavior. In contrast with the results of the last series of experiments, the following observation shows that possibly response to the local application of the antigen may be intensified by previous general sensitization.

Experiment 21.—Male, weight 570 gm. Olfactory lobes removed August 26 and the space left filled with melted paraffin. Sensitized subcutaneously with 0.33 c.c. of serum August 29. Received a prolonged inhalation of serum spray September 25, followed by no specific reaction. Inhalation was given again October 10, fifteen days later. A violent rapid dyspnea, which had not disappeared after an hour, immediately resulted. The treatment was repeated three times on alternate days, with identical response except that the latent period of reaction increased to a minute or two.

This experiment demonstrates again that response to the inhalation does not demand an intact olfactory apparatus.

I will now review rapidly the history of eighteen guinea-pigs, including individuals which were subcutaneously sensitized or normal and with olfactory lobes intact or removed. Half were treated primarily with instillations of serum into the nose and half with serum inhalations. Each group was again subdivided into two parts; the animals of one subgroup had serum dropped into the nose for four times on alternate days and those of the other for four times every fourth day.

The result was more or less active reaction with minor symptoms such as have already been described. After a resting interval of twelve days by the first group and of six days by the second group, which followed the last treatment in each, all of the nine "instillation" pigs were again given serum by the nose. To the local symptoms of nasal irritation and salivary secretion in certain animals was now added a more general reaction marked by more or less obvious dyspnea together with rattling, apparently bronchial râles. Of the two pigs in which the latter symptoms appeared, both had been subcutaneously sensitized and one had lost its olfactory lobes. Both râles and dyspnea were manifested only by animals which had received serum by the nose every fourth day. It is worth noting that when the group of animals treated in four sittings by serum dropped into the nose were given a like treatment eighteen days after the first dosage, the anaphylactic response was much more marked in animals which had received the preliminary instillations every *fourth* day.

In a parallel series of observations carried out with spray-inhalations, the reverse was noted; the strongest reactions occurred in animals receiving the four initial inhalations on *alternate* days. Five of the "instillation pigs" were given inhalations of serum on the day following the treatment which had produced so marked a reaction. The result was the production of a marked specific dyspnea in two of these animals. It is worth noting that of two pigs which had received no serum subcutaneously and from which the olfactory lobes had been removed, one responded by dyspnea to the spray and one did not. Of the two pigs not operated on, likewise without subcutaneous serum, neither responded. This experiment shows again that local sensitization of one part of the respiratory tract involves sensitization of the rest, though, as will be pointed out presently, there are marked local signs which distinguish the dyspnea produced by inhalation of serum in spray from that caused by its instillation in the nose.

Rapid dyspnea was the one sign of anaphylaxis observed in the inhalation experiments. It could be produced in nearly all animals, but some individuals responded much more readily than others. One animal which was made dyspneic by the inhalation, failed to react when sprayed daily, until the eighth day, when it responded again. In general, the daily administration of inhalations produced no response, though one pig which had received its first inhalation about two weeks previously responded each time to inhalation given every forty-eight hours. Of four animals which had received four sprayings on alternate days, from October 10 to 16, only one had shown marked reaction. They received another inhalation October 26 and each responded strongly — in fact the dyspnea in two cases was of desperate urgency.

Of these animals only two had been sensitized with serum subcutaneously. One of them had been deprived of olfactory lobes.

Five pigs which had received four inhalations from October 10 to 22 were likewise treated with the spray, October 26, but all responded very feebly. These animals were again given inhalations, November 2, and the dyspneic response was decidedly more vigorous though still much less marked than in the group treated after a longer passive interval. These results suggest, of course, the similar findings when anaphylaxis is studied through subcutaneous injections given at close intervals.

In a previous experiment it was shown that guinea-pigs sensitized by serum dropped into the nose could be made dyspneic at once by subjecting them to a spray of serum. The converse of this experiment was now performed. Four pigs that had reacted to the spray by dyspnea were given serum by the nose. In one there was reaction with only minor symptoms, but in the other three after long latent periods, five to ten minutes, rattling râles developed, which seemed to emanate from both the bronchi and the nose; there was also more or less cough.

As already mentioned, there is a marked difference in the quality of the anaphylactic response to the serum spray and serum instillation. In animals subjected to the former there are no râles, however violent the dyspnea. In animals responding strongly to the instillation, râles, which may be very loud and lasting, may occur with a variable element of dyspnea. The difference depends, probably, on the volume of secretion excited; that is, when a pig sensitized by instillation responds to the spray it is with a dry dyspnea; when a pig sensitized by the spray responds to instillation of serum droplets it is with a moist dyspnea. In later observations it was found that, in the shock resulting from the toxic intravenous injection, the influence of the "local sign" of the site of sensitization still held good. A pig which had been sensitized by the spray breathed very fast in its anaphylactic throes but developed no râles. Others which had been sensitized by instillation developed râles with, usually, less rapid breathing under the same conditions.

All the animals employed in these experiments were finally submitted to the supreme test of intravenous injection of serum. By this means it was sought to determine to what degree sensitization of the body could be developed by the peripheral application of serum, if at all, and also whether such application could essentially modify sensitization already induced by serum injected under the skin. The intravenous injections were given from twenty-nine to thirty days after beginning of the local treatment and after general sensitization had certainly been secured. Of the twenty and more animals available, four survived the first intravenous injection of serum.

Of eleven pigs treated by nasal instillation of serum three survived the first "toxic" injection. One of these belonged to a group of three from which the olfactory nerves and lobes had been removed but which had received no serum subcutaneously. This animal had been given serum by the nose four times at intervals of four days, from October 9 to October 21, and again on October 27. The creature had manifested plain signs of sensitization. Treated with serum spray, October 28, it became violently dyspneic. It was given 0.25 c.c. of serum intravenously, November 10. The animal was badly shocked in a manner peculiarly different from the ordinary anaphylactic seizures, that is, there were no clonic convulsions but the respiration was exceedingly rapid and made audible by râles. After about an hour, when the animal had apparently recovered, it suddenly suffered a fleeting twisting convulsion of the body. Thirteen days later, November 23, this animal received a second intravenous injection of more than 0.5 c.c. of serum. Great shock resulted with, at the outset, no sign of convulsion except clonic twistings. The respiration was very rapid and bronchial and nasal râles were loud. Finally, after sixteen days, December 9, a third intravenous injection of about 0.75 c.c. of serum was given. There was no anaphylactic reaction but great muscular weakness. Slight clonic twitchings set in after several hours, the weakness increased and the animal died in about twenty hours. Animals of this class also differed from those in ordinary anaphylactic reaction in that they appeared to be conscious even while lying on the side in deepest shock.

Of the other two "instillation pigs" that survived intravenous injection, both belonged to a group of three normal animals which had neither been operated on nor received serum subcutaneously. Their local treatment was similar to that of the last animal described except that neither was sprayed. Both of these animals, especially the second, had manifested slight but apparently unmistakable anaphylactic reaction to serum dropped into the nose. The first of the two was given 0.33 c.c. of serum intravenously November 8. The creature remained phenomenally quiet throughout the injection. There was no reaction whatever. The injection was repeated with 0.5 c.c. of serum, November 24: result, violent convulsions and typical death. I am inclined to interpret this case as further evidence that local sensitization may be achieved without producing any demonstrable general sensitization. The second surviving pig of this lot had especially reacted to instillation of serum by abundant secretions of saliva, an apparent sign of sensitization. Given an intravenous injection of 0.5 c.c. of serum, November 23, there was no reaction whatever (the animal was a female far advanced in pregnancy). Sixteen days later, the animal having borne a litter of young a week previously, a second intravenous injection of nearly 0.5 c.c. of serum was given. There was no reaction except for rapid, jerky breathing and a few râles. Special stress deserves to be laid on the fact that this animal had achieved its wonderful power of self-protection by a course of treatment which had provoked exceedingly slight signs of anaphylaxis.

The single "inhalation-pig" that survived an intravenous injection of serum belonged likewise to a group of three which had neither been subcutaneously sensitized nor operated on. This animal did not react to repeated inhalation treatments until several had been given; then the response was slight but positive as to anaphylaxis. November 8, 0.5 c.c. of serum was given intravenously. The reaction was moderate but distinct. At the outset respiration was deepened and there were slight convulsive movements. Then the breathing became very rapid, interrupted by occasional very deep breaths, and so continued for half an hour. There were no râles as in the instillation pigs. November 24, sixteen days later, the treatment was repeated. Deep, rapid respiration with strangling cough came on at once. The animal died in five minutes *without having exhibited respiratory râles or any convulsions.*

It will be noted that none of the animals which had been previously sensitized by the subcutaneous administration of serum survived the toxic injection. The conclusion is that general sensitization so produced is not essentially modified by the efficient antigen applied to the peripheral epithelium, although general sensitization is undoubtedly achieved in this way. That this non-interference of the serum, peripherally applied, with the previous general sensitization, is not dependent on the time intervals of its application, seems shown by the fact that six "instillation" and four "spray" pigs received a course of seven daily treatments extending to within three days of the toxic injection; but only one survived it: In other cases the interval between the last local treatment and the toxic injection extended to more than twelve days. It is clear also that the olfactory apparatus, as far as represented by the olfactory lobes and intracranial nerves, is not essential to the systemic effects of serum locally applied. In fact, the normal animals apparently resisted general sensitization in an active way except as to the secretion of saliva. Of a group of animals reacting in about the same way to local treatment, one might survive and the others succumb to the toxic injection.

There was nothing in the results obtained by me to suggest any change in the respiratory epithelium resembling the "phenomenon of Arthus" (increasingly morbid local changes following repeated subcutaneous injections), which has been carefully investigated by Nicolle.[21] This subject was not, however, definitely investigated.

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[21] Nicolle, M.: Ann. de l'Inst. Pasteur, 1907, xxi, 128.

The statements of Friedberger, Ishioka and Busson in regard to pneumonic changes in the lungs of sprayed animals were, to a degree, confirmed. Such lungs at necropsy frequently revealed air-free hemorrhagic areas of limited extent. The affected portions when removed would sink in water, but they were soft and not resistant as in pneumonic consolidation. The post mortem change was by no means constant among sprayed pigs and was also found in animals dying from toxic injections, which had not been sprayed at all.

POSSIBLE ATROPHY OF THE OLFACTORY EPITHELIUM

Because of its importance I venture mention of a theme on which investigation was started but abandoned early in this work. In animals deprived of their olfactory lobes and even in some under other and functional conditions, there seemed to be a well-marked atrophy of the olfactory mucous membrane as disclosed by cutting away the roof of the nasal cavities. The subject was pursued no further than to give a basis for special research.

THE EFFECT ON TUBERCULOUS GUINEA-PIGS OF TUBERCULIN APPLIED TO THE PERIPHERAL EPITHELIUM

It was, of course, a surface thought that some useful therapeutic purpose might be served by treating a systemic affection through the peripheral epithelium. Tuberculous guinea-pigs were the subjects and the old tuberculin of Koch was the remedy. Six young guinea-pigs were inoculated with what proved to be a very attenuated culture of tubercle bacilli, kindly furnished me by Dr. G. B. Webb of Colorado Springs, July 25. Three of the animals were inoculated in the peritoneum and three beneath the skin. Two were used as controls and four were treated. The treatment consisted in dropping into the mouth of two subjects, in such a way as to excite the maximum taste-sensations, or in instilling into the nose (two subjects) dilutions of old tuberculin usually of from 0.5 to 1 per cent. Treatment given was from every day to every fourth day. Treatments were begun more than six weeks before the inoculations and were continued for more than two months afterward. Superficial observation could detect no particular reaction to the treatments except the excitement of slight dyspnea by spraying (which was practiced later). One of the treated pigs had to be killed, October 23, because of a tuberculous swelling occluding the urethra. The other pigs all gained in weight and were sacrificed for specific purposes nearly four months after their inoculation with tubercle bacilli. Post-mortem examination left no manner of doubt as to the effect of treatment: The extent and intensity of the tuberculous processes were much greater in the treated animals than in the controls.

DISCUSSION AND SUMMARY

Certain facts recorded in this investigation seem to furnish evidence which must be considered in further discussions of the old problem of the physiological requirements in ventilation. The trend of scientific opinion has lately been to ascribe the deleterious properties of rebreathed air solely to the untoward physicial conditions of heat and humidity usually involved. Rosenau and Amoss[22] recently published experiments tending back to the old "chemical view" of the noxiousness of rebreathed air. Their work has been controverted in literature not available to me.

The observations, detailed above, on the desensitization of guinea-pigs when exposed to the smell of horses, seem to establish beyond question, if such proof were needed, that animal effluvia when inhaled can produce at once profound systemic disturbance. It is usually taken for granted that "ventilation" has the same biological import for all people. On the contrary, it may well be that people suffering from various ailments may find in rebreathed air noxal elements specifically related to their infections (as did my guinea-pigs in the stable). Such a conception, of course, vastly complicates the biological consideration of ventilation. For many years I have noticed in carrying out physical examinations of the sick that the subjects of pulmonary tuberculosis appeared especially prone to avoid, as far as possible, the inhalation of the examiner's breath; it has seemed to me an instinctive effort toward specific self-protection.

Evidence has been brought forward which indicates a peculiar immunological relation between the central nervous system, or at least the brain, and the body. The brain can be sensitized and desensitized an indefinite number of times without essentially changing the susceptibility of the body (Besredka records three desensitizations in one animal within a few days). This desensitization of the brain after horse-serum injections may be brought about by a number of different agencies,[22] the specific antigen, as used by Besredka, or something allied to it and contained in the effluvia of horses, or, as I have shown, by cutting the olfactory nerves, lacerating the brain tissue or even by setting up mechanical vibrations in it. Rapid desensitization of the brain is marked by a more or less profound nervous shock followed by a brief period of antianaphylaxis during which the animal is absolutely protected from the poisonous antigen. The nerve impulses producing this remarkable somatic change must operate on the living tissues. It appears probable that these nerve impulses cause the tissues, as it were, to open their receptors for the specific antibody in the blood.

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22. Rosenau and Amoss: Jour. Med. Research, 1911, xxv, 35.

23. Kolle and Wassermann: Handbuch der pathogenen Mikroorganismen, ii, Part 2, p. 1086.

If this "allergin" is removed from the circulation an animal has become essentially normal as regards reactivity to that antigen. Fixed in the tissues the allergin combines with more or less antigen contained therein and we witness a degree of shock proportional thereto. It is significant that all observers seem to agree that the allergin diminishes greatly or disappears from the circulation during the phase of antianaphylaxis.[24] According to the conception presented here the allergin is released from the tissues after a longer or shorter interval and, when returned to the circulation, susceptibility to the antigen is restored.

The widely accepted view of Friedberger[25] that antianaphylaxis depends on the saturation of the anaphylactic antibody with the newly introduced antigen cannot explain the condition when caused by brain mutilation; nor does this author's conception of the two states of non-specific and specific antianaphylaxis clear the matter. In fact, Bessau[26] makes a strong stand against Friedberger's theory and concludes that antianaphylaxis results from a reaction of the organism through which its irritability is depressed as regards the anaphylactic poison. In the masterly and lucid monograph of the Vaughans[27] it is held that the important factor which determines the refractory state of the reinjected animal "is the changed relation between the amount of ferment and the substrate," that is, the small amount of antibody remaining in the blood of the antianaphylactic animal becomes functionally inoperative in the presence of a great excess of antigen. This view, also, fails to account for the facts I have detailed. Evidence has been developed to show that the irritability of the brain, using this term in a broad physiological sense, is to an extraordinary extent dependent on olfactory stimuli. The teleological interpretation of these coordinations is irresistible. An animal smells many agents to which his body is sensitized and which, if eaten, would act as poisons *per se,* but through the olfactory sense the brain is sufficiently stimulated by the odor of the antigen to discharge impulses which set up in the body a state of antianaphylaxis during which the intrinsically poisonous substance may be ingested with impunity. The reaction of my guinea-pigs in the stable gives substantial support to such a conception. The possible relations of these conceptions to human physiology, psychology and surgery are obvious. The experiments with local applications of serum to the nose or by inhalation of a spray show clearly that sensitization of the respiratory epithelium develops after a definite latent period whose length does not appear to be influenced by previous general sensitization of the body.

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[24] See the valuable paper by Anderson and Frost, Bull. Hyg. Lab., U. S. P. H. S., 1910, No. 64.

[25] Friedberger: Ztschr. f. Immunitätsforsch., 1909, ii, 208.

[26] Bessau, G.: Centralbl. f. Bakteriol., 1911, lx, 637.

[27] Vaughan, V. C., Vaughan, V. C., Jr., and Vaughan, J. W.: Protein Split Products in Relation to Immunity and Disease, 1913, p. 312.

In contrast with this relative independence of central and peripheral sensitizations it is found that sensitization of the nasal respiratory tract involves the pulmonary epithelium, and *vice versa,* though each reacts with its own "local sign." The local reactions of the animal inevitably suggest that local anaphylaxis is a state of active resistance against absorption of the antigen. Transferring this idea to bacterial focal infections in the interior of the body, we get a more reasonable explanation of the beneficial results which often follow the injection of antigenous bacterial bodies; these can come into intimate contact with tissues capable of antibody formation from which the bacteria of the infective foci are debarred. Finally, the proof is once more absolute that serum dropped into the nose or given by inhalation sensitizes the body irrespective of the olfactory apparatus. The obvious explanation of the fact is that the antigen is absorbed by the circulation, as is supposed to be the case when serum is introduced into the rectum.[28] But "obvious explanations" are especially dangerous. Unfortunately, I have not been able to show that such peripheral application of the antigen in any way influences the reactions of a subcutaneously sensitized animal to the toxic intravenous injection. This seems a surprising fact in view of the accepted teaching that repeated injections of sublethal doses of serum produce in an animal a resistance, if not full immunity. That some peculiar status is occupied by the phenomena induced by application of serum to the respiratory epithelium seems shown by the fact that in two cases unsensitized guinea-pigs, from one of which the olfactory lobes had been removed, were somatically sensitized by this means and that they thereafter withstood several toxic injections separated by intervals of about two weeks. Experimental analogies have been presented for the anaphylactic phenomena of hay-fever and bronchial asthma. It is shown that both a general and a local sensitization are to be considered, interdependent, but each having an autonomy.

CONCLUSIONS

Briefly summarized, the following conclusions may be drawn:

1. Guinea-pigs sensitized to horse-serum may be desensitized by residence in a horse-stable. It is probable that this reaction may be rapidly achieved through the olfactory sense or more slowly by absorption through the respiratory mucous membrane. The period of anti-anaphylaxis is of less than two days' duration. The converse of this,

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[28] Vaughan, V. C.: Vaughan, V. C., Jr., and Vaughan, J. W.: Protein Split Products, 1913, p. 259.

sensitization of normal guinea-pigs in stable air, I have not been able to achieve.

2. Removal of part of the brain of a sensitized guinea-pig produces much more severe shock than the same amount of injury in a normal animal. This shock is apt to be followed by a period of antianaphylaxis of short duration.

3. Section of the olfactory nerves within the cranial cavity preceding the brain operation by a day or more abolishes the tendency to shock. Such nerve section in the normal animal also seems to reduce the shock arising from definite brain injury.

4. Depression of the olfactory sense may be produced through cocain and the symptoms of poisoning with this drug resemble those of anaphylaxis.

5. The body as a whole may be sensitized through the peripheral application of horse-serum after a definite latent period. The time required to sensitize the peripheral epithelium has not been found to be materially altered by previous general sensitization. A normal animal sensitized by local treatment may resist large intravenous injections of serum repeated at intervals of two weeks.

6. Sensitization of one area of the respiratory epithelium involves sensitization of the rest, though the local signs of expression are different.

7. The evidence indicates that local anaphylaxis, induced through the periphery, precedes the development of general sensitization.

8. Tuberculous guinea-pigs were made worse when treated by instillations or sprays of old tuberculin.

Besides the expression already made regarding Dr. Powell, it is a pleasure to acknowledge my indebtedness to my colleagues, Dr. W. C. Mitchell and Dr. P. Hillkowitz, for many favors, and to Dr. Auer of the Rockefeller Institute for hints as to technic.

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METABOLISM IN DEMENTIA PRAECOX *

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The findings reported in this paper are the result of work suggested by Dr. H. D. Singer, director of the institute, and begun by A. F. Wussow in this laboratory. Pighini[1] and Statuti[2] claimed from their data that the metabolism of dementia praecox was not normal. Wussow[3] and Barnes[4] did not obtain results that confirmed the findings of Pighini and Statuti. Folin[5] found no evidence of an abnormal metabolism in dementia praecox.

TESTS

The plan of the tests was to determine the income and the outgo of nitrogen, sulphur, phosphorus, calcium and magnesium in cases of dementia praecox. Tests were made at various times of the year and various diets were used (Table 1).

The method of preparing and preserving the food used in these tests made it possible to have but one sample of food for analysis and to give the patient a constant diet. For example, when hamburger was used as a part of the diet, sufficient very finely ground hamburger was cooked and then again very finely ground and mixed. Weighed amounts sufficient for a meal were put in ice-cream boxes and stored in a room which was maintained below 0 C. (32 F.). In the preparation of a meal one package of hamburger was put into a bowl with a small amount of water, set in a steam oven and warmed. Coffee, when used, was prepared by making up a liter or more of a very concentrated solution of commercial soluble coffee. Ten cubic centimeters of this were sufficient to make two cups of coffee. This amount was put into a pitcher with 20 c.c. of condensed milk and when the meal was ready to take to the ward, a couple of cups of boiling distilled water were added to each pitcher.

There were many difficulties to be overcome in doing metabolism work in cases of dementia praecox. One of the difficulties was with the feces. Cases of chronic or temporary constipation were frequently met.

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* From the Illinois State Psychopathic Institute.

* Submitted for publication Feb. 16, 1914.

[1] Pighini: Arch. Neurol. and Psychiat., 1909, iv, 220.

[2] Statuti: Am. Jour. Insanity, 1910, lxvii, 299.

[3] Wussow: Institution Quarterly of Illinois, March 31, 1913, p. 71.

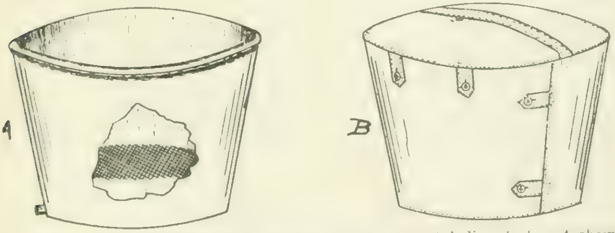
[4] Barnes: Am. Jour. Insanity, 1909, lx, 591.

[5] Folin, quoted by Wussow: The Institution Quarterly of Illinois, March 31, 1913.

TABLE 1.—DAILY DIET IN METABOLISM TESTS IN FIVE CASES OF DEMENTIA PRAECOX

Patient	Preliminary Test	Test Proper	Breakfast	Dinner	Supper
G. G.	Sept. 30-Oct. 4	Oct. 4-10	Graham crackers, peanut butter, butterine, agar.	Same as breakfast.	Same as breakfast.
A. S.	Dec. 13-14	Dec. 14-20	Rice (boiled with milk), jelly (containing English walnuts), sugared agar.	Omelet (of ham, egg, cheese and milk), sugared agar.	Same as breakfast.
M. P.	Feb. 4-10	Feb. 10-15	(Ham - egg - cheese - milk) - omelet, graham crackers, peanut butter, butterine, agar, milk.	Same as breakfast.	Same as breakfast.
S. K.	Aug. 16-21	Aug. 21-29	Soda crackers, peanut butter, agar sauce.	Soda crackers, hamburger, agar sauce.	Graham crackers, peanut butter, agar sauce.
F. L.	Nov. 13-27	Nov. 27-Dec. 4	Coffee, condensed milk, egg omelet, graham crackers, agar sauce.	Coffee, condensed milk, hamburger, graham crackers, agar sauce.	Coffee, condensed milk, peanut butter, crackers, agar sauce.

A clear demarcation of the feces was many times prevented by soft or scanty stools. To overcome constipation, to insure frequent and copious bowel movements and to obtain a sharp marking of feces, agar was fed in all of the described tests. It takes considerable determination for a normal person to eat 10 gm. of shredded agar three times a day for two weeks, and consequently trouble was encountered in attempting to feed such an amount to disinterested insane persons. Patient G. G. was induced to eat 7 gm. of ground shredded agar at each meal when it was mixed with peanut butter and butterine, and spread on crackers. A number of failures followed the attempts to feed agar in this way to other patients. Patient A. S. took the agar when it was ground and coated with crystal sugar. The most palatable form of agar which has yet been prepared by us and which was used in the tests on Patients S. K. and F. L., was made by passing shredded agar through a sausage-grinder, moistening it with water and mixing with ground apple-sauce. This leaves the small pieces of agar tender enough to take away the straw-like consistency.



Urine and feces collector used in dementia praecox metabolism tests. *A* shows galvanized shelf which holds the feces, allowing urine to pass through; *B*, collector in canvas case.

Much difficulty was at first encountered in the collection of urine and feces separately or at all. All tests were made on women patients. Many refused to use either bed-pan or urinal, or both. If the patient did not object to using the bed-pan and urinal, often the collections were spoiled by the passage of both urine and feces at once into the bed-pan. These difficulties were all overcome by the construction of a collector, which is shown in the illustration.

Immediately after the passage of the excretions, the urine was drawn off into a bottle and the collector put into the canvas case and brought to the laboratory. Carmin was used as feces marker in obtaining the feces resulting from the test periods of feeding. The difficulty of getting the patient's bladder completely emptied at the end of each day was not overcome.

The patient in each case was kept out of bed all day and taken daily for a walk of about two miles in the open air. All of the cases were examples of dementia praecox. Patients G. G., A. S. and F. L. were of the chronic type. Patients S. K. and M. P. were of the subsiding acute type.

I am indebted to Dr. H. D. Singer and Dr. S. N. Clark for the following summaries of the cases.

REPORT OF CASES

CHRONIC STAGE OF HEBEPHRENIC DEMENTIA PRAECOX

Case 1.—Patient F. L. has been in the Kankakee State Hosptal since January, 1904, and but little information is obtainable concerning her early life and the onset of the mental disorder. Her mother had been "slightly insane" for from fifteen to eighteen years. The patient was thought normal, married and had two children. In 1901, at the age of 32, she became depressed over the death of a child and following this became gradually more restless, excited and abusive and was treated at this hospital from August to December of that year. She was readmitted in January, 1904, and when received at the hospital was clear mentally, restless, irritable, experienced sense-falsifications with occasional violent reaction, and felt herself under outside influence. This early period of episodic restlessness, excitement and irritability apparently continued until 1907, when it was noted for the first time that she had become demented. She has since been indifferent, inactive and careless and untidy in appearance, with occasional episodes of noisy restlessness lasting a few days or weeks. She appears smiling, occasionally laughs and shows some stereotyped mannerisms such as suddenly pulling up her clothing. The metabolism test was performed in November and December, 1913, while patient was in a period of complete quiescence.

Case 2.—Patient G. G., aged 25, was admitted to the Kankakee State Hospital on Aug. 22, 1912, with but scanty anamnesis. The mental picture had persisted with but little change for at least four years at that time. It was characterized by a general lack of interest in her surroundings with occasional outbursts of unexplained irritability, neglect of personal appearance and occasional uncleanliness. It was impossible to employ her steadily and for the most part she sat smiling to herself or wandered slowly and aimlessly. She appeared to be quite clear and to recognize her surroundings, but gave no connected information. Speech and actions were desultory with many oddities and stereotypies. There were no evidences of disease of the body organs. When admitted, the patient showed hemic murmur, but it has since disappeared. At the time of the test the picture was as described above and there has been no material alteration since.

Case 3.—Patient A. S. was admitted to the Kankakee State Hospital, Dec. 9, 1910, aged 23. Very little is known of her early life, but she was considered an average child and graduated from common school at 14. She then went to work in a factory, but about two years later quietly gave it up and remained more or less indifferently at home. She became more and more careless and indifferent, developed certain peculiarities, such as touching various objects, putting odds and ends in her mouth, wandering away from home, etc., and probably experienced some sense falsifications, but without acute reactions. When admitted presented some physical signs suggestive of a tuberculous process in the lung, but there have been no cough, fever or loss of weight to suggest an active condition. The mental picture has been one of marked absence of spontaneity, a smiling compliance with all requests, indifference to personal appearance and cleanliness, and to the situation, in spite of full clearness. Answers to questions show much desultoriness of thought with some *vorbeireden*. Except for a period of a few weeks beginning in February, 1911, when she became semistuporous, had to be spoon-fed and was more or less inaccessible though without rigidity of muscles, the picture outlined above has persisted unchanged. The metabolism test was made in December, 1912, while the patient was in this stationary condition.

SUBSIDING STAGE OF ACUTE KATATONIC DEMENTIA PRAECOX

CASE 4.—Patient M. P. was admitted to the Kankakee State Hospital, Dec. 28, 1912. Her mother has suffered from some psychosis, probably dementia praecox, since 1907. The patient was born in 1882 and is described as bright intellectually, with special interest in music, but always very nervous, self-conscious and irritable. She had no friends or confidants, was much alone and professed a hatred for male society. During the summer of 1912 she became depressed and later more restless with many odd acts and increasing inaccessibility. She also experienced auditory hallucinations. In December, 1912, she passed into a state of mutism and complete inactivity with some waxy rigidity of limbs, and was in this condition when admitted. The metabolism studies were undertaken in February, 1913, during this phase of katatonic stupor. During the earlier part of the tests she remained entirely mute and inaccessible, but towards the end of the two weeks she began to be slightly more active and to obey simple requests. The improvement continued subsequently but the patient has remained stilted and affected in speech and act, more or less indifferent to her surroundings, her friends, and her personal cleanliness, with outbursts of unmotived restless irritability and even violence, which occasionally interrupt a usual appearance of smiling indifference.

CASE 5.—Patient S. K. was admitted to the Kankakee State Hospital, July 25, 1913, aged 20. This patient is Bohemian and it has been impossible to obtain much anamnesis. She is described as an unusually bright child with no previous illness. In July, 1913, she became depressed and was admitted in a condition of marked katatonic stupor with absolute mutism and entire lack of spontaneous movement, with often some waxy rigidity and command automatism. Food was swallowed when placed in the mouth, but the patient paid no attention to flies or to other stimuli. August 1 she spoke for the first time since admission, but did not speak again before the 15th. The metabolism test was begun August 16 and continued until August 29, by which time it was possible to obtain a few answers to questions. She has since improved steadily and was allowed to return to her friends Nov. 16, 1913, having gained 23 pounds, though she still showed a lack of spontaneity with some vacuity and a failure to grasp the fact and nature of her illness. Conversation with her was very difficult owing to language differences.

Analyses of a composite of the daily food, finely ground and mixed, were made for nitrogen, sulphur, phosphorus, calcium and magnesium. The urine for the entire period was well mixed and analyses made of the mixture for the different forms of nitrogen and sulphur, in addition to the analyses made on the food. A composite of the total feces of the period was made in each case, and the same analyses made as on the food. The methods used are the following: Kjeldahl method for nitrogen, Folin's sodium-peroxid and Benedict's methods for total sulphur, Folin's methods for total sulphates and inorganic sulphates in urine, McCrudden's method for calcium and magnesium, Benedict's and Gephart's method for urea, Folin's method for ammonia, Folin-Shaffer method for uric acid and Folin's colorimetric method for creatinin. The official method of the Association of Official Agricultural Chemists was used to determine the phosphorus after its oxidation. The oxidation in the case of the urine was with aqua regia, and in the case of foods and feces by ignition followed by digestion with concentrated nitric acid for four hours.

The accompanying tables contain the results of the five tests.

TABLE 2.—NITROGEN EXPRESSED IN GRAMS PER DAY

Type	Patient	Length of Test Days	Food	Urine	Feces	Balance
Chronic. .	F. L.	7	19.0230	7.6966	1.1616	10.1648+
	G. G.	6	18.2122	10.5703	1.5340	6.1078+
	A. S.	6	12.5496	11.8703	1.9313	1.2520—
Subsiding, acute . .	M. P.	4	16.0290	7.2058	0.7714	8.0518+
	S. K.	8	10.4437	7.1181	0.9619	2.3637+

TABLE 3.—DISTRIBUTION OF URINARY NITROGEN EXPRESSED IN GRAMS PER DAY

		Nitrogen				
Type	Patient	Total	Urea	Ammonia	Creatinin	Uric Acid
Chronic. .	F. L.	7.6966	6.8366	0.1514	0.3674	0.1433
	G. G.	10.5703	9.5321	0.2328	0.1093	0.0722
	A. S.	11.8703	10.5489	0.4349	0.2489	0.0423
Subsiding, acute . .	M. P.	7.2058	5.3741	0.4426	0.1245	0.1035
	S. K.	7.1181	5.8038†	1.0097	0.3382	0.0738

TABLE 4.—DISTRIBUTION OF URINARY NITROGEN EXPRESSED IN PERCENTAGE OF TOTAL NITROGEN

		Nitrogen				
Type	Patient	Total	Urea	Ammonia	Creatinin	Uric Acid
Chronic. .	F. L.	100	88.87	1.97	4.78	1.86
	G. G.	100	90.17	2.00	1.03	0.68
	A. S.	100	88.82	3.66	2.09	0.37
Subsiding, acute . .	M. P.	100	74.70	6.15	1.73	1.44
	S. K.	100	81.83†	14.19	4.78	1.04

† Determination was made on urine several days old; therefore the results are probably high.

TABLE 5.—EXCRETION OF SULPHUR EXPRESSED IN GRAMS PER DAY

Type	Patient	Length of Test Days	Food	Urine	Feces	Balance
Chronic. .	L. F.	7	1.9620	0.7155	0.4395	0.8070+
	G. G.	6	1.7216	0.3143	0.4378	0.9695+
	A. S.	6	1.0174	0.7691	0.4210	0.1727—
Subsiding, acute . .	M. P.	4	2.1645	0.9768	0.5282	0.6895+
	S. K.	8	0.9756	0.5930	0.5233	0.1407—

TABLE 6.—DISTRIBUTION OF URINARY SULPHUR EXPRESSED IN GRAMS PER DAY

		Sulphur				
Type	Patient	Total	Total Sulphate	Inorganic Sulphate	Neutral	Ethereal Sulphate
Chronic. .	F. L.	0.7155	0.6321	0.5469	0.0834	0.0852
	G. G.	0.3142	0.2293	0.2756	0.0847	
	A. S.	0.7691	0.4550	0.4421	0.3140	0.0129
Subsiding, acute . .	M. P.	0.9768	0.2858	0.2936	0.6910	
	S. K.	0.5930	0.4631	0.4291	0.1299	0.0340

TABLE 7.—DISTRIBUTION OF URINARY SULPHUR EXPRESSED IN PER CENT. OF TOTAL SULPHUR

		Sulphur				
Type	Patient	Total	Total Sulphate	Inorganic Sulphate	Neutral	Ethereal Sulphate
Chronic..	F. L.	100	88.30	76.30	11.64	11.90
	G. G.	100	72.99	87.72	27.02	
	A. S.	100	59.15	57.47	40.82	1.68
Subsiding, acute..	M. P.	100	29.26	30.06	70.76	
	S. K.	100	78.12	72.39	21.91	6.08

TABLE 8.—PHOSPHORUS EXPRESSED IN GRAMS PER DAY

Type	Patient	Length of Test Days	Food	Urine	Feces	Balance
Chronic..	F. L.	7	1.2825	0.4111	0.3798	0.4916+
	G. G.	6	2.2200	0.5369	1.1810	0.5021+
	A. S.	6	1.2960	0.7193	0.5676	0.0091+
Subsiding, acute..	M. P.	4	1.3552	......	0.2474	..
	S. K.	8	0.7625	0.3393	0.6347	0.2115—

TABLE 9.—CALCIUM EXPRESSED IN GRAMS PER DAY

Type	Patient	Length of Test Days	Food	Urine	Feces	Balance
Chronic..	F. L.	7	1.1003	0.2731	0.6978	0.1294+
	G. G.	6	2.4045	0.2272	1.8988	0.2785+
	A. S.	6	1.3068	0.2794	0.8368	0.1906+
Subsiding, acute..	M. P.	4	1.0960	0.5954	0.3032	0.1974+
	S. K.	8	0.6699	0.2472	0.4314	0.0087—

TABLE 10.—MAGNESIUM EXPRESSED IN GRAMS PER DAY

Type	Patient	Length of Test Days	Food	Urine	Feces	Balance
Chronic..	F. L.	7	0.6789	0.1281	0.2875	0.2633+
	G. G.	6	0.6313	0.1002	0.4931	0.0380+
	A. S.	6	0.3521	0.1031	0.2594	0.0104—
Subsiding, acute..	M. P.	4	0.4841	0.1161	0.1635	0.2045+
	S. K.	8	0.5356	0.0872	0.3302	0.1182+

TABLE 11.—DISTRIBUTION OF VARIOUS ELEMENTS EXPRESSED IN RELATION TO NITROGEN VALUED AT 100

Type	Patient	Food	Urine	Feces	Urine and Feces	Balance
		Sulphur				
Chronic..	F. L.	10.32	9.29	37.82	13.04	7.94+
	G. G.	9.45	2.97	28.54	6.21	15.87+
	A. S.	8.11	6.48	21.80	8.62	13.79+
Subsiding, acute..	M. P.	13.50	13.56	68.45	18.87	8.56+
	S. K.	9.34	8.33	54.42	13.82	5.95—
		Phosphorus				
Chronic..	F. L.	6.73	5.34	32.68	8.93	4.84+
	G. G.	12.19	5.08	76.78	14.20	8.22+
	A. S.	10.32	6.06	29.40	9.32	0.73—
Subsiding, acute..	M. P.	8.45	.....	32.06	.....	
	S. K.	7.30	4.77	66.01	12.06	8.95—
		Calcium				
Chronic..	F. L.	5.78	3.55	60.05	10.96	1.27+
	G. G.	13.20	2.15	123.78	17.57	4.56+
	A. S.	10.41	2.35	43.34	8.08	15.23—
Subsiding, acute..	M. P.	6.84	8.26	39.29	11.27	2.45+
	S. K.	6.42	3.47	44.86	8.40	0.37—
		Magnesium				
Chronic..	F. L.	3.57	1.66	24.74	4.69	2.59+
	G. G.	34.66	0.95	32.14	4.90	0.62+
	A. S.	2.80	0.87	13.43	2.62	0.83+
Subsiding, acute..	M. P.	3.02	1.61	21.19	3.50	2.54+
	S. K.	5.13	1.22	34.34	5.17	4.99+

DISCUSSION OF RESULTS

Total Nitrogen.—Table 2 indicates nothing of particular interest concerning the nitrogen distribution. With an intake of 12.5 gm. of nitrogen as in the case of Patient A. S., a negative balance is hardly to be expected. The excessive amount of nitrogen in the urine, which was responsible for this negative balance is more or less constant for this patient as shown in a previous test.[6]

Nitrogen Partition, Urea Nitrogen.—The urea nitrogen in the several cases varied from 5.37 to 9.53 gm. daily. These values are within the range of the normal urea output, but nearer the minimum than the maximum limit. When the patients are grouped according to the two classes of dementia praecox, one is immediately struck with the fact that, as far as the urea nitrogen is concerned, each class seemed to have a field of variation of its own. The chronic cases excreted from 6.84 to 10.55 and the acute cases from 5.37 to 5.80 gm. of urea nitrogen. The same class difference is indicated in Table 4 in which the urea nitrogen is expressed in per cent. of the total urinary nitrogen. In the chronic cases it is from 88.8 to 90.2, while in the acute cases it is from 74.7 to 81.8 per cent.

Folin[7] shows that the urea output is governed to some extent by the protein intake. Folin fed 118 gm. of protein and found a urea-nitrogen output of 14.7 gm. which constituted 87.5 per cent. of the total urinary nitrogen. When he fed 6 gm. of protein, the urea-nitrogen excretion decreased to 2.2 gm., making up only 61.7 per cent. of the total urinary nitrogen. The question now arises as to whether or not in our cases the class differences in the output of urea nitrogen in grams and in per cent. were not due to a difference in the nitrogen intake. If this were true, there should be no constant difference between the two classes of patients in the number of grams of urea nitrogen excreted per gram of nitrogen ingested, and in the per cent. of urea nitrogen making up the total urinary nitrogen per gram of nitrogen ingested. That this is the case in both of the relations is shown by the following figures for Patients F. L., G. G., A. S., M. P. and S. K., respectively, 0.359, 0.523, 0.841, 0.335 and 0.556 gm. of urea nitrogen per gram of nitrogen ingested, and 4.67, 4.95, 7.08, 4.66 and 7.84 per cent. of total urinary nitrogen in the form of urea nitrogen per gram of the total nitrogen intake. Since these figures do not show any definite distinction between the two classes of patients, and since it is well known that the urea nitrogen is governed to some extent by the nitrogen intake, we must conclude that in this test the differences in urea excretions were due to the differences in the nitrogen intake.

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[6] Ross, Ellison L.: Some Forms of Urinary Nitrogen Affected by the Administration of Desiccated Thyroid to Dementia Praecox Patients, The Archives Int. Med., 1913, xii, 746.

[7] Folin: Quoted by Lusk in Science of Nutrition, p. 138.

Ammonia Nitrogen.—Normally ammonia nitrogen varies from about 0.2 to 1 gm. per day. The amount varies in normal individuals with the diet, depending on the amount of protein ingested and on the amount of acid-forming constituents and alkali metals of the diet. In pathological cases excessive ammonia output indicates an increased acid formation within the organism. Von Noorden[8] states that when the ammonia nitrogen of the urine does not exceed from 8 to 10 per cent. of the total nitrogen intake it cannot be said to be abnormal.

In this test the ammonia nitrogen varied from 0.15 to 1.01 gm. per day, entirely within the normal so far as the absolute quantities are concerned. The difference between the two classes of dementia praecox in this is distinct, but not great enough to prohibit the explanation of the difference on the grounds of differences in the character of the food.

In Table 4 the ammonia nitrogen is expressed in per cent. of the total nitrogen of the urine. Expressed in this way, ammonia nitrogen makes up from 2.0 to 14.2 per cent. of the total amount in the urine. Von Noorden[8] considers this manner of expressing the amount of ammonia nitrogen of no value. That this is true is indicated by Folin's[7] test, cited before, in which 118 gm. were fed with an output of 16.8 gm. of urinary nitrogen and 0.49 gm. of ammonia nitrogen, making up 3.0 per cent. of the urinary nitrogen, whereas when 6 gm. of protein were fed, 3.6 gm. of nitrogen appeared in the urine, of which 0.42 gm., or 11.3 per cent. was ammonia nitrogen. In these two tests there were about equal quantities of ammonia nitrogen expressed in grams, but nearly four times as much in the second test as in the first, if measured by the per cent. of the total urinary nitrogen, which made up from 60 to 90 per cent. of the variable urea nitrogen. It is an interesting fact, however, that in the acute cases a greater per cent. of nitrogen in the form of ammonia nitrogen was excreted than in the chronic cases.

If the ammonia nitrogen were expressed in per cent. of the total nitrogen ingested we would have for Patients F. L., G. G., A. S., M. P., and S. K., the following values: 0.80, 1.28, 3.46, 2.76, and 9.71 per cent. These figures show a tendency in the acute cases to the excretion of the greater amount of ammonia nitrogen. The average of the values for the acute cases, 6.23 per cent., is larger than the average of any two cases in the chronic group and considerably larger than the average of all of those in the chronic group, 1.85 per cent. According to Von Noorden this variation not being outside of from 8 to 10 per cent., could not be said to be abnormal.

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[8] Von Noorden: Metabolism and Practical Medicine, i, 106.

Creatinin and Uric Acid Nitrogen.—No distinction can be detected between the two classes of patients by their output of creatinin and uric acid nitrogen. The amounts of creatinin and uric acid nitrogen are within the range of normal persons, according to Schaffer,[9] Hawk,[10] Neubauer, P. Munk and C. Voit,[11] Van Noorden[12] and Folin.[13]

Total Sulphur.—Table 5 indicates the distribution of the total sulphur. The intake varied from 0.97 to 2.16 gm. per day. The urinary sulphur had a greater variation, from 0.31 to 0.98 gm. per day. The fecal sulphur was remarkably constant for the two classes of patients. In the chronic class it was from 0.42 to 0.44 gm. and in the acute class from 0.52 to 0.53 gm. per day. Undoubtedly the greater part of this sulphur in the feces was in the indigestible agar, which contains about 1 per cent. of sulphur. The balances of sulphur are such as might be expected to accompany the nitrogen balances given in Table 2, except in the case of Patient S. K., who showed a positive nitrogen balance, but a negative sulphur balance. Although the character of the diet given in Table 1 is usually considered a well-balanced one, the analysis of the food and feces seems to indicate that the available sulphur occurred in an insufficient quantity in the diet of S. K.

Table 11 indicates the sulphur distribution relative to the total nitrogen distribution, the latter taken as a standard being evaluated as 100. The sulphur-nitrogen relation in the foods of the five patients varied considerably—from 8.11 to 13.50 per cent. This variation is undoubtedly due to the agar, which is poor in nitrogen and contains about 1 per cent. of sulphur.

The sulphur-nitrogen relation for the urines is interesting in the wide range of variation of from 2.97 to 13.56 per cent. The same large variation exists for the feces and for the total outgo. In the case of the urine, feces and total outgo, the sulphur-nitrogen relation of the two classes of patients materially differs. The average of all of the values or any two of the values for the chronic cases is less than the average for the acute cases. It therefore may be concluded from these tests that in the subsiding acute cases of dementia praecox there is a tendency to excrete more sulphur in proportion to nitrogen in both urine and feces than in the cases of chronic dementia praecox. Whether or not this tendency is outside of the limits of normal variation cannot be determined from the data available.

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[9] Shaffer: Quoted by P. B. Hawk in Practical Physiological Chemistry, Ed. 3, p. 270.

[10] Hawk: Quoted by P. B. Hawk in Practical Physiological Chemistry, Ed. 3, p. 266.

[11] Neubauer, Munk P., and Voit, C.: Quoted by Von Noorden in Metabolism and Practical Medicine, i, p. 127.

[12] Von Noorden: Metabolism and Practical Medicine, i, p. 115.

[13] Folin: Quoted by Lusk in Science of Nutrition, pp. 138-364.

Sulphur Partition.—Total Sulphate-Sulphur.—The patients in this test excreted in the urine from 0.23 to 0.63 gm. of sulphur in the form of sulphates. These amounts made up from 29.26 to 88.30 per cent. of the total sulphur in the urine. While the total sulphate-sulphur of the urine is dependent on both diet and physical condition of the subject, Hawk[14] states that normally about 2.5 gm. of sulphuric acid or about 0.8 gm. of sulphur are excreted per day in the sulphate form. Folin[5] gives the total sulphate-sulphur output of two normal cases on a purin-free diet. The first case gave an average of 1.14 gm. or 94.2 per cent. of the total urinary sulphur. The second case gave 0.87 gm. or 86.9 per cent. of the total urinary sulphur. Mandel and Lusk[16] found that a normal subject, on a six-day test, excreted, for every 100 gm. of nitrogen ingested, an average of 6.24 gm. of sulphur in the form of sulphates. Our patients, taken in the order in which the cases are arranged in the tables, excreted, for every 100 gm. of nitrogen ingested, 3.32, 1.26, 3.62, 1.83 and 4.45, or an average of 2.90 gm. of sulphur in the form of sulphates. While the above comparisons, made with the total sulphate output in these cases of dementia praecox, have not been closely comparable for reasons of differences of diet, subjects and conditions of subjects, they have shown that the patients of our test did not excrete normal amounts of sulphate sulphur.

Inorganic Sulphates: Tables 6 and 7 show the amount of sulphur in the form of inorganic sulphates in the urine to have varied from 0.27 to 0.55 gm. per day, or from 30.06 to 87.72 per cent. of the total urinary sulphur. There is also a suggestion of a difference between the two classes of dementia praecox in the amounts of inorganic sulphates excreted. The average of the two lowest values in the chronic cases is 0.3588 gm., or 72.59 per cent. of the total urinary sulphur, and the average in all three cases is 0.4215 gm., or 73.83 per cent. of the total urinary sulphur, while the average in the subsiding acute cases is 0.361 gm., or 51.22 per cent. of the total. There is an overlapping of values in the two classes, so that the class difference must be considered small. As to the normality of the values as a whole for the inorganic sulphate sulphur output, there is little question. The only data at hand for comparison are those of Folin.[15] On a purin-free diet, Folin's patients averaged 1.028 gm., or 86.2 per cent., and 0.80 gm., or 78.7 per cent. of the total sulphur. According to these figures the chronic patient's output of inorganic sulphate would be nearly normal so far as the percentage of the total sulphur is concerned, but low in absolute quantities. Compared in the same way, in the acute cases the patients were below normal both in absolute weight of inorganic sulphate sulphur and in its relation to the total urinary sulphur.

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[14] Hawk: Practical Physiological Chemistry. Ed. 3, p. 291.

[15] Folin: Quoted by Lusk in Science of Nutrition, p. 364.

[16] Mandel and Lusk: Quoted by Von Noorden in Metabolism and Practical Medicine, iii, 613.

Neutral-Sulphur.—The neutral-sulphur output of our patients is especially interesting in that it confirms Pighini's[1] findings. The absolute amount varies from 0.0834 to 0.6910 gm., making up from 11.64 to 70.76 per cent. of the total urinary sulphur. While there is some overlapping of values in the two classes of patients, there seems to be a distinct tendency in the acute cases to the excretion of the greater amount of neutral-sulphur. The average of the two highest values in the chronic class is 0.1883 gm., making up 33.92 per cent. of the total sulphur, and the average of all three chronic cases 0.1607 gm., or 26.49 per cent. of the total sulphur of the urine, while the average output in the acute cases was 0.4104 gm., or 46.33 per cent. of the total urinary sulphur.

Sherman[17] states that normally from 5 to 15 per cent. of the total urinary sulphur is neutral-sulphur. Von Noorden finds that the neutral sulphur normally makes up from 14 to 25 per cent. of the total urinary sulphur. Folin's cases averaged 5.8 and 13.1 per cent., or 0.14 and 0.10 gm., of neutral-sulphur. These figures indicate that in the chronic cases an amount of neutral-sulphur very close to the limit of normal subjects was excreted, and that the acute cases were quite abnormal in this respect.

Ethereal Sulphates.—The data on the ethereal sulphate-sulphur output are not satisfactory or sufficient to be of any considerable importance. The tendency seems to be toward a low percentage for this form of sulphur.

Phosphorus.—Table 8 gives the distribution of phosphorus in the food, urine, feces, and the balance. The intake varied from 0.76 to 2.22 gm. Sherman[18] states that in normal subjects about 1.2 gm. are necessary for a phosphorus balance to result, but that a phosphorus balance has been obtained on as low as 0.90 gm. per day. From these facts it is evident that Patient S. K. did not receive sufficient phosphorus for a normal person. Therefore the negative phosphorus balance in this patient was to have been expected. In the urine the phosphorus seems to have been more normal in all cases. Von Noorden[19] states that normally the ratio $P_2O_5 : N = 1 : 7$. In our cases the ratio varies from 1:7.1 to 1:9.1.

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[17] Sherman: Chemistry of Food and Nutrition, p. 268.

[18] Sherman: Chemistry of Food and Nutrition, p. 278.

[19] Von Noorden: Metabolism and Practical Medicine, iii, 817.

Calcium.—The calcium distribution shown in Table 9 is relatively a normal one. The intake varied from 0.6699 to 2.4045 gm. per day. Sherman[20] states that the normal body requires from 0.7 to 1.0 gm. of CaO, or expressed in terms of Ca, from 0.5 to 0.7 gm. per day. The calcium intake of Patient S. K. was the only one which approached the minimum limit. That it was her smallest calcium requirement is shown by her very small negative balance. The amount of calcium in the urine varied from 0.2272 to 0.5954 gm., which, according to von Noorden,[21] is normal. No difference between the two classes of patients can be detected from the absolute amounts excreted or the amounts relative to the nitrogen given in Table 2.

Magnesium.—Renvall[22] asserts that man normally needs 0.45 gm. of magnesium per day. Langworthy[23] estimates the normal bodily requirement of magnesium to be from 0.18 to 0.30 gm. per day. Our patients received from 0.3521 to 0.6789 gm. per day. According to Langworthy's standard all patients received sufficient magnesium. According to Renvall's standard all but one of our patients had a sufficiency of this element and that patient had a small negative balance. The magnesium content of the urines was quite constant, varying from 0.0872 to 0.1281 gm. The feces content was quite variable because of the relative richness of the agar in the food. The balances show nothing of importance. The absolute amounts and the relative amounts of magnesium to the nitrogen in the urines, feces and balances do not show any differences between the two classes of dementia praecox.

SUMMARY

Five cases of dementia praecox, three of them in a chronic and two in a subsiding acute phase of the disease, were used in the metabolism tests. Over a period of from four to eight days the exact income and outgo of total nitrogen, different forms of nitrogen, total sulphur, different forms of sulphur, phosphorus, calcium and magnesium were determined.

The metabolism of total nitrogen was found to be within the limits of normal with the possible exception of one case.

The urea nitrogen of the urine was variable but remained normal.

The ammonia nitrogen of the urine varied within the limits found in normal cases. In the acute cases a tendency was exhibited to excrete more of this form of nitrogen than in the other class of patients.

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[20] Sherman: Chemistry of Food and Nutrition, p. 288.

[21] Von Noorden: Metabolism and Practical Medicine, iii, 39.

[22] Renvall: Quoted by von Noorden in Metabolism and Practical Medicine, i, 428.

[23] Langworthy: Quoted by E. B. Forbes in Bull. Ohio Experiment Station, No. 201, p. 165.

The amounts of creatinin and uric acid nitrogen obtained in these cases of dementia praecox coincide with the normal.

The metabolism of total sulphur is considered normal, with the acute cases showing a greater sulphur excretion, both in urine and feces, than the other class of patients.

The total sulphate-sulphur output, according to the data on normal cases cited by authorities, was below normal.

The inorganic sulphate-sulphur of the urine, according to data on normal subjects, was below normal in absolute quantities in both classes of patients, and lowest in the case of the acute class. The amounts of this form of sulphur expressed in percentage of the total urinary sulphur, were about normal for the chronic class but below normal for the acute group.

The urinary neutral-sulphur was practically normal for the chronic cases, but much above normal in the subsiding acute cases.

The ethereal sulphate findings were negative.

As to the meaning of these positive findings on the sulphur metabolism there is little question. In the chronic cases there was normal total sulphur, practically normal neutral sulphur, below normal total sulphate and possibly below normal inorganic sulphate. In the acute cases we have a normal, but a maximum normal, excretion of total sulphur, subnormal total sulphate, subnormal inorganic sulphate and supernormal neutral sulphur. E. Salkowski and Rudenko[24] state the well-known fact that an increased neutral-sulphur output at the expense of the sulphates is an indication of reduced power of tissue oxidation. Therefore it must be concluded from the sulphur data that in the acute cases the patients had lost to a certain degree their normal powers of oxidation. Also this is suggested in the patients in the chronic class by the subnormal sulphate output. That a reduced power of oxidation should occur in cases of acute dementia praecox is not surprising, since seemingly every bodily activity is decreased. That indol-acetic acid is very frequently found in the urines of dementia praecox patients[5] is evidence of a diminished power of oxidation.

The findings on phosphorus, calcium and magnesium were negative.

CONCLUSIONS

In these cases of dementia praecox the data show the following facts:

1. The metabolism of nitrogen, phosphorus, calcium and magnesium was normal in both classes of patients.

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[24] Salkowski, E., and Rudenko: Quoted by von Noorden in Metabolism and Practical Medicine, ii, 355.

2. The metabolism of sulphur, except in the excessive total sulphate output and possibly the inorganic sulphate output, was normal for the chronic cases.

3. The metabolism of sulphur in the acute cases was abnormal in that the excretion of total sulphur was maximum normal, the total sulphate and inorganic sulphate output were subnormal and the neutral sulphur of the urine was above normal.

4. The abnormalities in the sulphur metabolism of the acute forms indicate a reduced power of metabolic oxidation. The fewer and less pronounced abnormalities of sulphur metabolism in the chronic group suggest a similar, though less extensive deficiency, than in the case of the acute group.

THE TITRATION OF WASSERMANN REAGENTS *

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As the Wassermann test is considered, and should be, a quantitative reaction, the correct titration of the reagents, especially complement and amboceptor, is of the utmost importance.

Wassermann,[1] in the original communication, and Noguchi,[2] as well as other writers on the subject, recommend the titration of complement and amboceptor without the addition of the other factors. That is, these two factors are mixed in varying quantities with a suspension of corpuscles. On incubation the smallest amount of the factor which, with a fixed quantity of the other, is required to produce complete hemolysis, is considered as one unit. For the actual test twice the unit is used.

This method of titration is open to objection. Noguchi has pointed out that within certain limits complement and amboceptor are interchangeable. Further, it is a recognized fact that on the addition of patients' serum (whether positive or negative) or antigen, more complement or amboceptor is required to produce hemolysis than when neither of these factors is added. This is overcome by doubling the units of complement and amboceptor.

The objection is that the worker does not know that twice the amount of complement and amboceptor which are required to produce hemolysis without serum and antigen will just produce hemolysis with them; that is, of course, if the serum is from a non-luetic patient, and the worker does not know that, when just a small amount of the complement present is bound by a slightly positive serum, enough complement may be left to produce complete hemolysis, and a weakly positive test be changed to a negative.

The following method of titration of complement and amboceptor has been adopted by me in my Wassermann work:

Actual test conditions are imposed on the factors throughout. The human hemolytic system is employed. The method of preparing the reagents has been described in a previous article.[3]

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* Submitted for publication Dec. 8, 1913.

* From the Laboratory of Clinical Diagnosis, Medical Department, University of Arkansas.

[1] Deutsch. med. Wchnschr., 1906, xxxii, 745.

[2] Noguchi, H.: The Serum Diagnosis of Syphilis, Philadelphia, 1911.

[3] Thompson, Loyd Oscar: A Modified Wassermann, THE ARCHIVES INT. MED., 1913, xi, 512.

The corpuscle suspension is a 2.5 per cent. solution of washed human erythrocytes. The complement is a 10 per cent. solution of guinea-pig serum, while the amboceptor is a solution of the serum of a rabbit, which has been immunized to human corpuscles, and diluted according to the titrated value.

The corpuscle suspension is, of course, fixed and when amboceptor is titrated, it is necessary first to titrate the complement to be used against a known amboceptor, or to fix the dose of complement arbitrarily. The latter is the usual method and I choose 0.5 c.c. as the most common unit.

Fifteen tubes are required for the titration of amboceptor and eight tubes for controls. The controls are the same as those used in the actual test. In each of the fifteen tubes is placed 0.1 c.c. of a known negative inactivated serum, 0.5 c.c. of complement, 1 unit of antigen (diluted so that 1 unit = 0.1 c.c.), and the amount of physiological salt solution required to bring the total volume up to 2.5 c.c., as indicated in Table 1.

TABLE 1.—Titration of Amboceptor

Tube	Serum	Comp.	Ant.	NaCl	Amboceptor	Corp.	Total	Results
1	0.1	0.5	0.1	0.8	0.5 of 1:10,000	0.5	2.5	NH
2	0.1	0.5	0.1	0.7	0.6 of 1:10,000	0.5	2.5	NH
3	0.1	0.5	0.1	0.6	0.7 of 1:10,000	0.5	2.5	PH
4	0.1	0.5	0.1	0.5	0.8 of 1:10.000	0.5	2.5	PH
5	0.1	0.5	0.1	0.4	0.9 of 1:10,000	0.5	2.5	PH
6	0.1	0.5	0.1	1.2	0.1 of 1: 1,000	0.5	2.5	PH
7	0.1	0.5	0.1	1.1	0.2 of 1: 1,000	0.5	2.5	PH
8	0.1	0.5	0.1	1.0	0.3 of 1: 1,000	0.5	2.5	H
9	0.1	0.5	0.1	0.9	0.4 of 1: 1,000	0.5	2.5	H
10	0.1	0.5	0.1	0.8	0.5 of 1: 1,000	0.5	2.5	H
11	0.1	0.5	0.1	0.7	0.6 of 1: 1,000	0.5	2.5	H
12	0.1	0.5	0.1	0.6	0.7 of 1: 1,000	0.5	2.5	H
13	0.1	0.5	0.1	0.5	0.8 of 1: 1,000	0.5	2.5	H
14	0.1	0.5	0.1	0.4	0.9 of 1: 1,000	0.5	2.5	H
15	0.1	0.5	0.1	0.3	1.0 of 1: 1,000	0.5	2.5	H
16	0.0	0.5	0.0	0.5	1.0 of 1: 1,000	0.5	2.5	H
17	0.0	0.5	0.1	0.4	1.0 of 1: 1,000	0.5	2.5	H
18	0.0	0.5	0.1	1.4	0.0	0.5	2.5	NH
19	0.0	0.5	0.0	1.5	0.0	0.5	2.5	NH
20	0.0	0.0	0.1	0.9	1.0 of 1: 1,000	0.5	2.5	NH
21	0.0	0.0	0.1	1.9	0.0	0.5	2.5	NH
22	0.0	0.0	0.0	1.0	1.0 of 1:1.000	0.5	2.5	NH
23	0.0	0.0	0.0	2.0	0.0	0.5	2.5	NH

The tubes are now incubated one hour in the incubator or half an hour in the water-bath at 37 C., after which the amboceptor and corpuscles are added.

Tube 1 contains 0.5 c.c. of a 1:10,000 dilution of amboceptor and the amount is increased until Tube 15 contains 1 c.c. of a 1:1,000 dilution, or 0.01 c.c. of pure serum. The incubation is continued two hours in the incubator, or one hour in the water-bath at 37 C. At the end of this time the tube which contains the least amboceptor, which shows complete hemolysis, is determined and this amount of amboceptor is considered as 1 unit.

The titration of complement is similar except that here the amboceptor is the fixed quantity and the tubes contain increasing amounts of complement, as indicated in Table 2.

TABLE 2.—Titration of Complement

Tube	Ser.	Comp.	Ant.	NaCl	Amb.	Corp.	Total	Results
1	0.1	0.4	0.1	1.3	0.1	0.5	2.5	PH
2	0.1	0.5	0.1	1.2	0.1	0.5	2.5	PH
3	0.1	0.6	0.1	1.1	0.1	0.5	2.5	PH
4	0.1	0.7	0.1	1.0	0.1	0.5	2.5	H
5	0.1	0.8	0.1	0.9	0.1	0.5	2.5	H
6	0.1	0.9	0.1	0.8	0.1	0.5	2.5	H
7	0.1	1.0	0.1	0.7	0.1	0.5	2.5	H
8	0.0	1.0	0.0	0.9	0.1	0.5	2.5	H
9	0.0	1.0	0.1	0.8	0.1	0.5	2.5	H
10	0.0	1.0	0.1	0.9	0.0	0.5	2.5	NH
11	0.0	1.0	0.0	1.0	0.0	0.5	2.5	NH
12	0.0	0.0	0.1	1.8	0.1	0.5	2.5	NH
13	0.0	0.0	0.1	1.9	0.0	0.5	2.5	NH
14	0.0	0.0	0.0	1.9	0.1	0.5	2.5	NH
15	0.0	0.0	0.0	2.0	0.0	0.5	2.5	NH

In the actual performance of the test, one unit each of complement and amboceptor, and only one, is used. This is all that is required, since it has been determined that, with these amounts, we have secured complete hemolysis with a known negative serum, and if, with an unknown serum, we get any inhibition of hemolysis, we know that something has bound at least part of the complement, which indicates a positive reaction.

In the titration of antigen the first and most important point is to determine whether or not the antigen is hemolytic in an amount considerably in excess of the antigenic unit. This is determined by adding to a corpuscle suspension gradually increasing amounts of the antigen, as indicated in Table 3.

TABLE 3.—Titration of Antigen (Hemolytic Effect)

Tube	Ant.	Corp.	NaCl	Total	Results
1	0.5 of 1:100	0.5	1.5	2.5	NH
2	0.6 of 1:100	0.5	1.4	2.5	NH
3	0.7 of 1:100	0.5	1.3	2.5	NH
4	0.8 of 1:100	0.5	1.2	2.5	NH
5	0.9 of 1:100	0.5	1.1	2.5	NH
6	0.1 of 1: 10	0.5	1.9	2.5	NH
7	0.2 of 1: 10	0.5	1.8	2.5	NH
8	0.3 of 1: 10	0.5	1.7	2.5	NH
9	0.4 of 1: 10	0.5	1.6	2.5	NH
10	0.5 of 1: 10	0.5	1.5	2.5	NH
11	0.6 of 1: 10	0.5	1.4	2.5	NH
12	0.7 of 1: 10	0.5	1.3	2.5	NH
13	0.8 of 1: 10	0.5	1.2	2.5	NH
14	0.9 of 1: 10	0.5	1.1	2.5	NH
15	1.0 of 1: 10	0.5	1.0	2.5	NH
16	1.5 of 1: 10	0.5	0.5	2.5	PH
17	2.0 of 1: 10	0.5	0.0	2.5	H

Tube 1 contains 0.5 c.c. of a 1:100 dilution of antigen, while Tube 17 contains 2 c.c. of a 1:10 dilution, or 0.2 c.c. of pure antigen.

The tubes are now incubated for one hour in the water-bath at 37 C., and the one containing the largest amount of antigen in which there is no hemolysis is recorded.

Working with Dr. Gabby of the Psychopathic Institute at Kankakee, Ill., and Dr. Nichols of the Presbyterian Hospital, Chicago, I have shown that certain antigens, which have a marked hemolytic action when added to corpuscles alone, have this action inhibited when either human or guinea-pig serum is added in small quantity (0.1 c.c.).

The question naturally presents itself, whether or not such an antigen would be a safe one to use, since antigen is never used in a test without the presence of patients' serum and complement. I do not consider it safe, because if it is used, and the corpuscles are hemolyzed, it would not be known how much of the hemolysis is due to the amboceptor and complement, and how much to the antigen.

TABLE 4.—TITRATION OF ANTIGEN (ANTICOMPLEMENTARY VALUE)

Tube	Ser.	Comp.	Ant.	NaCl	Amb.	Corp.	Total	Results
1	0.1	0.5	0.5 of 1:100	0.8	0.1	0.5	2.5	H
2	0.1	0.5	0.6 of 1:100	0.7	0.1	0.5	2.5	H
3	0.1	0.5	0.7 of 1:100	0.6	0.1	0.5	2.5	H
4	0.1	0.5	0.8 of 1:100	0.5	0.1	0.5	2.5	H
5	0.1	0.5	0.9 of 1:100	0.4	0.1	0.5	2.5	H
6	0.1	0.5	0.1 of 1: 10	1.2	0.1	0.5	2.5	H
7	0.1	0.5	0.2 of 1: 10	1.1	0.1	0.5	2.5	H
8	0.1	0.5	0.3 of 1: 10	1.0	0.1	0.5	2.5	H
9	0.1	0.5	0.4 of 1: 10	0.9	0.1	0.5	2.5	H
10	0.1	0.5	0.5 of 1: 10	0.8	0.1	0.5	2.5	H
11	0.1	0.5	0.6 of 1: 10	0.7	0.1	0.5	2.5	H
12	0.1	0.5	0.7 of 1: 10	0.6	0.1	0.5	2.5	H
13	0.1	0.5	0.8 of 1: 10	0.5	0.1	0.5	2.5	H
14	0.1	0.5	0.9 of 1: 10	0.4	0.1	0.5	2.5	H
15	0.1	0.5	1.0 of 1: 10	0.3	0.1	0.5	2.5	PH

The second point to be determined is the anticomplementary effect of the antigen. In a good antigen this effect must not be evident in an amount considerably greater than the antigenic unit. A series of fifteen tubes is arranged as in Table 4, 0.1 c.c. of a known negative, inactivated serum is placed in each tube, one unit of previously titrated complement (usually 0.5 c.c.), increasing amounts of the antigen and enough salt solution to bring the total volume, when amboceptor and corpuscles are added, to 2.5 c.c. The tubes are now incubated for half an hour in the water-bath at 37 C., after which one unit of previously titrated amboceptor and 0.5 c.c. of corpuscles are added and the incubation continued for one hour. The tube which contains the largest amount of antigen in which hemolysis is complete is recorded.

The next and final point in the titration of antigen is the determination of the antigenic unit. This titration is identical with the determination of the anticomplementary value, except that instead of using a known negative serum, a known positive serum is employed. In fact, these two titrations may be, and usually are, carried out at one time. After the final incubation the tubes are placed in the ice-box for a few hours, when the tube is determined which contains the smallest amount of antigen in which inhibition of hemolysis is complete.

TABLE 5.—Titration of Antigen (Antigenic Unit)

Tube	Ser.	Comp.	Ant.	NaCl	Amb.	Corp.	Total	Results
1	0.1	0.5	0.5 of 1:100	0.8	0.1	0.5	2.5	H
2	0.1	0.5	0.6 of 1:100	0.7	0.1	0.5	2.5	PH
3	0.1	0.5	0.7 of 1:100	0.6	0.1	0.5	2.5	PH
4	0.1	0.5	0.8 of 1:100	0.5	0.1	0.5	2.5	PH
5	0.1	0.5	0.9 of 1:100	0.4	0.1	0.5	2.5	PH
6	0.1	0.5	0.1 of 1: 10	1.2	0.1	0.5	2.5	NH
7	0.1	0.5	0.2 of 1: 10	1.1	0.1	0.5	2.5	NH
8	0.1	0.5	0.3 of 1: 10	1.0	0.1	0.5	2.5	NH
9	0.1	0.5	0.4 of 1: 10	0.9	0.1	0.5	2.5	NH
10	0.1	0.5	0.5 of 1: 10	0.8	0.1	0.5	2.5	NH
11	0.1	0.5	0.6 of 1: 10	0.7	0.1	0.5	2.5	NH
12	0.1	0.5	0.7 of 1: 10	0.6	0.1	0.5	2.5	NH
13	0.1	0.5	0.8 of 1: 10	0.5	0.1	0.5	2.5	NH
14	0.1	0.5	0.9 of 1: 10	0.4	0.1	0.5	2.5	NH
15	0.1	0.5	1.0 of 1: 10	0.3	0.1	0.5	2.5	NH

The antigenic unit is that amount of antigen which is the average of the smallest amount which will completely inhibit hemolysis with a known positive serum, and the largest amount which will cause no inhibition with a known negative serum. For example, if we have found that 0.1 c.c. of the 1:10 dilution of antigen completely inhibits the hemolysis with a known positive serum, and 0.9 c.c. of antigen is the largest amount which does not inhibit hemolysis with a known negative serum, 0.5 c.c. is the antigenic unit.

ATTEMPTS TO PRODUCE SCARLATINA IN MONKEYS *

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Notwithstanding the numerous attempts to inoculate the lower monkeys with scarlet fever, the positive results reported, notably those of Cantacuzène[1] and Bernhardt,[2] have not been substantiated by others who have repeated the experiments of these observers. (Notes 1 to 4 give the complete recent literature.) Thus Landsteiner and Levaditi[3] inoculated thirty-five monkeys of five different lower species with exudate from the throat and with the blood and lymph-nodes of scarlet-fever patients, by local application to the fauces of the animals and by intravenous, intraperitoneal and subcutaneous injections of scarlet-fever products without obtaining a seemingly positive result. Klimenko,[4] making use of twenty monkeys of five lower species, was equally unsuccessful, although he included among his many experimental procedures that of Bernhardt, who claims to have produced the disease in fourteen out of nineteen aimals. Shortly after the publication of Cantacuzène's first papers, Dr. Park inoculated six monkeys with the blood of six fresh scarlet-fever cases, including several of the malignant type. The technic employed was the same as that described in Cantacuzène's report. The results[5] were completely negative. Our few experiments are given herewith as an additional contribution to the proof that this class of monkey is immune to the virus of scarlet fever when inoculated by any method heretofore made use of.

Some of the inoculations recorded had their inception in a laboratory accident: An assistant, while preparing the suspensions of streptococci for immunization of horses, sucked some of the suspension into her mouth. This accident occurred Oct. 24, 1912. On the morning of October 26, a beginning sore throat was noticed which became progressively worse during the day. The sore throat with general symptoms of prostration continued on October 28, tingling of the skin and arms and

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[1] Cantacuzène: Compt. rend. Soc. de biol., 1911, lxxi, 196 and 405.

[2] Bernhardt: Deutsch. med. Wchnschr., 1911, xxxvii, 791.

[3] Landsteiner, Levaditi and Prasek: Ann. de l'Inst. Pasteur, 1911, xxv, 754.

[4] Klimenko: Jahrb. f. Kinderheilk., 1913, lxxvii, 679.

[5] Unpublished.

chest was noticed, probably the beginning of the exanthem. When seen on the morning of October 29, a general pharyngitis was present, and a typical scarlatinal rash covered the arms, chest and abdomen, the legs being comparatively free. The temperature was 101.6 F., rising to 102 later in the day. During the next two days the temperature fell to normal and the throat and general symptoms disappeared. The subsequent course was uneventful, desquamation taking place in a typical manner. As far as could be determined, there had been no contact with a case of scarlet fever.

The streptococci in the suspension were the following:

Scarlet fever—throat, 4 strains, 2 hemolyzing, 2 green.
Mastoiditis—3 strains, 3 hemolyzing.
Puerperal sepsis—3 strains, 3 hemolyzing.
Pleurisy—1 strain, green.
Erysipelas—1 strain, hemolyzing.

EXPERIMENTS

EXPERIMENT 1.—Monkey No. 593, Java, female, Nov. 25, 1912, throat swabbed and sprayed with a heavy suspension of strains of streptococci previously mentioned. This suspension was used in all the experiments. The blood-counts taken in all will be found in the accompanying table. No change in throat or tongue was observed in any animal, no inclusion bodies (Döhle), were seen in any of the smears except in Experiment 3.

Observations.—The temperature, which was taken for ten days before the animal was used to determine the normal range, fluctuated between 100 and 101.4 F. After inoculatioon the temperature range remained the same, except for one rise to 102.2, November 28.

EXPERIMENT 2.—Dog-faced baboon A, male. Dec. 3, 1912, throat swabbed and sprayed with the suspension.

Observations.—The temperature fluctuated between 99.4 and 101.6 F. for eight days preceding inoculation. After inoculation the highest point was 101.8.

EXPERIMENT 3.—Dog-faced baboon B, female. Dec. 13, 1912, throat swabbed and sprayed with suspension.

Observations.—The temperature before injection was only taken for three days and ranged about 101 F. After injection it rose at times to 102 and twice to 102.2 F. Small dot-like inclusion bodies were occasionally noted, which were slightly more numerous December 4.

Results.—Mixed streptococci from scarlet fever and other sources which have been grown for some months on media, caused no perceptible reaction, when applied to the throat of monkeys.

EXPERIMENT 4.—Monkey 593, Macacus, female. Dec. 6, 1912, 2 c.c. of sterile 10 per cent. sodium citrate solution were drawn into a syringe, which was then used to take 25 c.c. of blood from a child ill four and one-half days with scarlet fever. The child showed a profuse rash over body, typical scarlatinal tongue and throat and enlargement of the cervical, inguinal and axillary lymph-nodes. The temperature at the time was 102 F. The blood was injected intraperitoneally into the monkey within a few minutes after withdrawal from the child.

Observations.—Before and after injection the range of temperature fluctuated between 101 and 102.2 F. December 10, 11, 12 and 13, the temperature ranged from 102 to 102.2 F. At no other time did the temperature remain at this height.

The noteworthy points in this experiment are that on the fourth day after the injection the temperature reached its highest point and remained high for four days. On the day preceding this rise the polynuclear percentage rose and during the four days of highest temperature continued its rise with that of the total count. As the monkey was menstruating at this time no weight can be placed on these changes. At best they were too slight to be even suggestive of a successful inoculation.

TABLE OF TOTAL NUMBER OF LEUKOCYTES AND PERCENTAGE OF POLYNUCLEARS IN EXPERIMENTS 1 TO 7

	Animal									
	593		A		B		593*		A*	
Days Before Inoculation	Leuk. No.	Polyn. %	Leuk. No.	Polyn. %	Leuk. No.	Polyn. %	Leuk. No.	Polyn. %	Leuk. No.	Polyn. %
8	—	—	12,600	43	—	—	—	—	—	—
7	—	—	15,600	27	—	—	—	—	11,500	38
6	13,850	59	13,150	40	—	—	—	—	—	—
5	10,500	67	—	—	—	—	—	—	—	—
4	12,000	63	11,000	33	—	—	10,500	57	10,500	44
3	12,500	64	—	—	—	—	—	—	—	—
2	13,000	65	—	—	11,000	48	10,700	53	—	—
1	10,500	64	14,000	40	14,000	35	—	—	—	—
Day of Inoculation 0	13,300	68	—	—	—	—	—	—	—	—
Days After Inoculation										
1	13,600	59	12,400	36	12,500	54	11,300	56	13,000	43
2	11,300	66	12,000	42	—	—	—	—	—	—
3	—	—	—	—	13,000	46	12,500	70	9,000	54
4	11,200	62	11,500	38	11,000	50	16,500	68	9,000	37
5	—	—	—	—	13,000	33	14,000	70	10,400	31
6	—	—	—	—	—	—	10,500	61	—	—
7	10,500	57	10,500	44	—	—	12,500	68	—	—
8	—	—	—	—	10,200	—	9,000	59	9,100	—
9	10,700	53	—	—	—	—	—	—	—	—
10	—	—	—	—	—	—	—	—	—	—
11	—	—	—	—	—	—	9,300	52	—	—
12	—	—	—	—	—	—	—	—	—	—
13	—	—	—	—	—	—	—	—	—	—
14	—	—	—	—	—	—	—	—	—	—
15	—	—	—	—	—	—	10,300	—	—	—

* Second inoculation.

EXPERIMENT 5.—Dog-faced baboon A. Dec. 13, 1912, 25 c.c. of blood were taken from a child of 13, five days ill with scarlatina, who showed a typical rash and scarlatinal throat and tongue. The temperature at the time was 100 F. The blood was injected intraperitoneally into the monkey immediatel after withdrawal from the child.

Observations.—The temperature reached 101.8 before injection, but as a rule fluctuated closely around 101 F. After injection the range was between 101 and 102 F., giving in the chart the appearance of a slight transient rise.

Result.—The intraperitoneal injection of 25 c.c. of blood into a macacus monkey was followed by a slight rise in temperature and a coincident increase in the total and polynuclear leukocyte count; this rise, however, was slight and probably due to other causes. A similar injection into a baboon was followed by no reaction.

Experiment 6.—Dog-faced baboon 12, female. March 31, 1913, swabs were smeared with the discharge from ears, throat and nose of seven children, ill from four to fifty-five days with scarlet fever alone or with scarlet fever and subsequent complications. The material on the swabs was washed off in sterile normal saline solution. This suspension was filtered through a Berkefeld filter, the first filtrate being thrown back on the filter and saline passed through the filter after the suspension had passed through. Forty c.c. of filtrate was obtained, which was bacterially sterile, and this was injected intraperitoneally.

Observations.—The temperature rose to 102 F. the second day after injection. The normal range for this animal was about 101 F., occasionally rising half a degree higher.

Experiment 7.—Dog-faced baboon 12, female. April 21, 1913, swabs were collected as in the preceding experiment. These were washed off in saline, giving a total of 4 c.c. suspension. This was sprayed and swabbed on the animal's throat.

Observations.—The temperature did not rise above 101.6 F.

Results.—The intraperitoneal injection of bacteria-free material from scarlet-fever cases and the direct application to throat of the same type of material without filtration, were followed by no reaction.

SUMMARY

The attempt to produce scarlet fever in monkeys and baboons by the faucial inoculation of streptococcus cultures or unfiltered exudates and discharges from scarlet-fever cases, as well as the intraperitoneal injections of filtrates of such exudates and discharges and of large quantities of blood, gave negative results.

GERMAN MEASLES (RUBELLA): AN EXPERIMENTAL STUDY *

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Investigations as to the nature of German measles are totally lacking. This is probably due to the fact that this disease is mild and so rarely encountered in hospital wards. The only opportunity afforded for a systematic study from a laboratory standpoint is the occurrence of an epidemic in an institution where children are housed in large numbers. An occasion of this kind—an epidemic attacking fifty or more children in an infant asylum—led to the present investigation, which includes a bacteriological study of the blood, inoculations of blood into monkeys with the object of producing the disease, and a cellular examination of the blood during the period of incubation of the disease.

In four instances the blood was obtained for bacteriological examination. In three of the cases the rash had been present for less than twenty-four hours, and in the fourth for about thirty-six hours; in two the temperature of the child was above the average, that is to say, between 102 and 103 F. So that it may be said that I was able to obtain the blood in severe cases as well as at the very onset of the disease. The latter circumstance would appear of particular importance when we remember that the virus of measles has been found with regularity only in the early period following the stage of exanthem. Numerous cultures made on mediums containing serum and hemoglobin showed no growth whatsoever. Other cultures were made by Dr. Zingher, whom I wish to thank in this connection, according to the method developed by Noguchi for the cultivation of the spirochete of syphilis; the medium contains two parts of salt-free agar, one part of ascitic fluid, fresh kidney tissue, and is covered with liquid petrolatum to insure anaerobic conditions. It was not found possible to obtain any growth from the inoculation of the blood in our cases. The tubes were incubated for some weeks.

An attempt was made to produce this disease in monkeys. Four *Macacus rhesus* monkeys were inoculated with blood obtained from four different cases. In two instances the blood was from the same source as that used for purposes of cultivation. In all cases the rash had existed less than twenty-four hours; in most the temperature was high when the blood was withdrawn. Following is a summary of the protocols:

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* From the Research Laboratory, Department of Health, New York City.

* Submitted for publication Jan. 8, 1914.

CASE 1.—Feb. 7, 1913. Child which developed rash during the night; temperature normal.

Three c.c. of citrated blood inoculated intraperitoneally into Monkey 1. The temperature was followed for four weeks. Although it frequently rose to 103 or over, there was no sudden rise or fall.

CASE 2.—March 3, 1913. Rash seen on child for first time this morning; temperature 101 F.

Five c.c. of blood obtained from right jugular vein, and inoculated intraperitoneally a few hours later into Monkey 2. The course of the temperature is shown in the accompanying chart. It will be noticed that there is a definite rise occurring on the nineteenth day after inoculation and lasting for about forty-eight hours.

CASE 3.—March 6, 1913. Child with rash for past twelve hours; temperature 101 F.

Four c.c. inoculated intraperitoneally into Monkey 3. For three weeks temperature varied between 101.1 and 102.3 F. No rash.

CASE 4.—March 8, 1913. Temperature of patient 101.3 F. when blood was withdrawn. Rash had existed about twelve hours.

Eight c.c. of blood inoculated intraperitoneally into Monkey 4; cultures also taken. For the next three weeks the temperature ranged between 101.3 and 103 F. No exanthem.

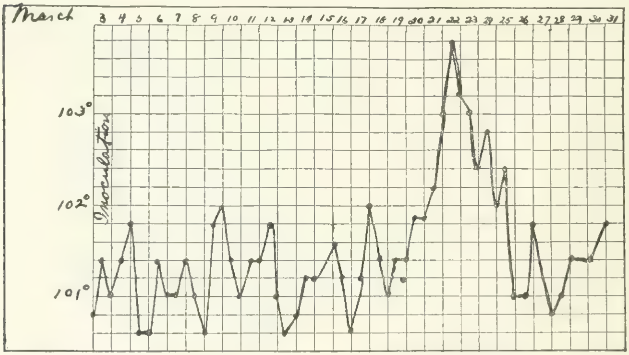

Chart of temperature of monkey (Case 2) inoculated with blood from early case of rubella.

It will be seen that in each instance from 3 to 8 c.c. of blood was inoculated intraperitoneally. In no case did the rash develop. In view of the fact, however, that this appears so rarely and faintly in experimental measles, it was hardly anticipated that we would succeed in producing a rash experimentally in rubella. Our attention, therefore, was closely directed to the course of the temperature. In only one instance was there a rise in temperature, following a considerable period of incubation (see chart). In the others there was no such rise. In view of the fact that the temperature of monkeys is somewhat unstable, too great significance should not be accorded this rise of temperature. In general, it may be stated that there is danger in placing too great reliance on a rise of temperature as the sole criterion of the production of a disease in monkeys. If the rise is sudden and the period of incubation carefully controlled, however, this method of study is of value.

Although there have been no cultures whatsoever made of the blood in German measles and no inoculation experiments on monkeys, there have been, as might be supposed, some previous investigations as to the number and type of leukocytes in this disease. Hildebrandt and Thomas[1] found a leukopenia at the onset of the exanthem, and an increase of the lymphocytes, as well as an increase in the large Türk cells. Michaels,[2] as the result of an investigation of eighty cases of rubella, also found a leukopenia in the majority of cases. These studies, however, were carried out after the rash had appeared; and the only study which has taken cognizance of the blood in the earlier stages of the disease was one by Plantenga.[3] Our investigation concerned itself entirely with the blood during the incubation period. This was very easily carried out in the institution; for as soon as rubella developed, blood-smears were taken daily from the healthy children in the ward and were laid aside for examination in the event of some of these children developing the disease. In this way, in numerous instances, consecutive blood examinations were carried out before and up to the appearance of the rash. The following data show the results of these examinations, which were kindly carried out for me by Dr. Jerome Zuckerman:

1. H. B., 2 years old. Exanthem May 2.

Per Cent. of	April 28	April 29	April 30	May 2
Polyn.	55	66	53	50
Lymph.	20	22	35	35
L. mono.	11	5	8	10
Eosinoph.	3	4	4	4
Basoph.	1	3	0	1

2. L. S., 3½ years old. Exanthem May 2.

Per Cent. of	April 28	April 29	April 30	May 2
Polyn.	59	51	54	41
Lymph.	28	33	36	45
L. Mono.	5	9	9	9
Eosinoph.	8	7	1	4
Basoph.	..	..	..	1

3. S. S., 5 years old. Exanthem May 2.

Per Cent. of	April 28	April 29	April 30	May 2	May 12
Polyn.	49	46	50	31	50
Lymph.	35	39	40	55	34
L. Mono.	7	5	4	5	8
Eosinoph.	5	10	5	6	4
Basoph.	4	0	1	3	4

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[1] Hildebrandt and Thomas: Ztschr. f. klin. Med., 1906, lix, 444.

[2] Michaels, M.: Arch. Pediat., 1908, xxv, 598.

[3] Plantenga: Arch. de méd. d. enf., 1903, vi, No. 3.

4. M. G., 2 years old. Exanthem June 14.

Per Cent. of	June 11	June 13	June 14	June 19
Polyn.	43	33	34	53
Lymph.	46	57	56	42
L. Mono.	7	7	7	5
Eosinoph.	4	3	3	

5. G. S., 2 years od. Exanthem June 19.

Per Cent. of	June 14	June 18	June 19
Polyn.	40	34	29
Lymph.	51	62	63
L. Mono.	8	1	7
Eosinoph.	..	3	1

6. R. K., 2½ years old. Exanthem June 19.

Per Cent. of	June 14	June 18	June 19
Polyn.	52	35	45
Lymph.	45	59	51
L. Mono.	3	6	4

7. W. S., 2 years old. Exanthem June 19.

Per Cent. of	June 14	June 18	June 19
Polyn.	54	46	45
Lymph.	41	52	54
Eosinoph.	5	2	1

It is evident that *in almost all cases of German measles there was a definite increase in the lymphocytes even preceding the appearance of the exanthem.*

It would seem that this premonitory lymphocytosis might be of value to institutions in heralding the fact that infection has taken place, and in facilitating the segregation of infected from non-infected children, and thus, perhaps, in limiting the spread of an epidemic. That there is a lymphocytosis at the time of the appearance of the rash may also serve to differentiate rubella from scarlet fever, a disease with which it is sometime confounded, but which is associated with an increase of polynuclear cells in its early stage.

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THE DIFFERENTIAL DIAGNOSIS OF THE INTESTINAL ENTAMEBAS OF MAN *

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The observations on the parasitic amebas that have been made within recent years have emphasized the importance of distinguishing between the species parasitic in the intestine of man, and it is the purpose of this contribution to give, as briefly as possible, the chief morphological points on which such a differentiation must rest, and the technic that I have found most helpful in demonstrating the morphology of these parasites. In order that what follows may be clear, a brief review of our present knowledge of the intestinal entamebas of man is necessary.

HISTORICAL ACCOUNT

In 1903, Schaudinn[1] described and differentiated two species of entamebas parasitic in the intestine of man. One of these, the cause of the disease known as amebic dysentery, he named *Entamoeba histolytica,* while the other, a harmless commensal, he named *Entamoeba coli.*

In 1905, while studying these parasites in soldiers invalided home from the Philippine Islands with dysentery, I confirmed Schaudinn's observations, and published my results in the summer of that year.[2] In that paper I detailed the morphology of both species and the results of experiments on kittens with these entamebas, being the first to confirm Schaudinn's statements regarding the pathogenicity of *E. histolytica,* and the non-pathogenicity of *E. coli* to these animals. At that time I suggested that the ameba concerned in the causation of dysentery be named *Entamoeba dysenteriae,* but as the name *dysenteriae* was afterward shown by Stiles[3] to be merely a synonym of *coli,* I adopted Schaudinn's name *histolytica* for this parasite.

Hartmann,[4] in 1906, confirmed Schaudinn's classification of the intestinal entamebas of man, but for several years the distinction between *E. coli* and *E. histolytica* was disputed by most authorities, largely owing

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* From the U. S. Army Central Department Laboratory.

* Submitted for publication Jan. 8, 1914.

[1] Schaudinn, F.: Arb. a. d. k. Gsndhtsamte, 1903, xix, 547.

[2] Craig, Charles F.: Am. Med., 1905, ix, 854, 897, 937.

[3] Stiles, C. W.: Proc. Am. Public Health Assn., 1905, xxx, 292.

[4] Hartmann, M.: Arch. f. Protistenk., 1909, xviii, 207.

to the observations of Musgrave and Clegg[5] on the amebas they secured on artificial culture-mediums and their conclusion that these amebas were identical with those found parasitic in the intestine of man, and "that all amebas are or may become pathogenic."

In 1907, Viereck[6] described a species of ameba observed in certain cases of dysentery which differed markedly from the original description of *E. histolytica* and which he regarded as a new species, naming it *Entamoeba tetragena.* His observations were confirmed by Hartmann,[7] Werner,[8] Darling,[9] Whitmore,[10] and myself, but further study has shown that in reality *E. tetragena* is identical with *E. histolytica,* a portion of the life cycle of the latter parasite having been erroneously described by Schaudinn, Hartmann and myself, as well as by others.

Walker[11] was actually the first to point out that *E. tetragena* is identical with *E. histolytica,* and all of the work that has been accomplished by other investigators since his paper appeared has simply been confirmatory of his conclusions, and at present all students of the subject, who have had sufficient material on which to work, are agreed that two well-defined species of entamebas occur in the intestine of man, *E. histolytica* and *E. coli.* The first is the cause of amebic dysentery, while the second is a harmless commensal, occurring in the intestines of a varying percentage of individuals, in both health and disease, in almost every part of the world.

In 1905 and later, I stated[12] that the parasitic amebas of man had not been cultivated, nor could they be cultivated, on the ordinary culture-mediums employed by those who claimed to have cultivated these organisms from the feces or other material, and this statement has been amply confirmed by nearly every subsequent investigator. At present there is no adequate proof that a single species of entameba has ever been cultivated on any artificial medium. A few observers still claim that the amebas that they have succeeded in cultivating are identical with the entamebas of the human intestine but their claims have been refuted by many investigators and it has been conclusively shown that the amebas so cultivated are entirely distinct from the entamebas of man, and have nothing to do with the production of dysentery.

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[5] Musgrave, W. E., and Clegg, M. T.: Rep. Bur. Govt. Lab., Biol. Lab., Manila, 1904, No. 18.

[6] Viereck, H.: Arch. f. Schiffs u. Tropen-Hyg., 1907, xi, 1.

[7] Hartmann, M.: Arch. f. Protistenk., 1912, xxiv, 163.

[8] Werner, H.: Indian Med. Gaz., 1909. xliv, 241.

[9] Darling, S. T.: Jour. Trop. Med., 1912, xv, 1.

[10] Whitmore, E.: Arch. f. Protistenk., 1911, xxiii, 7.

[11] Walker, E. L.: Philippine Jour. Sc., Sec. B, 1911, vi, 259.

[12] Craig, Charles F.: Am. Med., 1905, ix, 854, 897, 937; Jour. Infect. Dis., 1908, v, 324; The Parasitic Amebae of Man, Philadelphia, 1911, p. 58. Jour. Infect. Dis., 1913, xiii, 1.

Since 1905 I have consistently maintained the specificity of *E. histolytica* and *E. coli,* and in my first paper, and since, have insisted that it is possible to differentiate these two species in material containing them. I have also proved that neither of these parasites can be cultivated on ordinary culture-mediums, and that, while *E. histolytica,* when fed to kittens or injected into the rectum, produces typical amebic dysentery and even liver abscesses, *E. coli* is harmless to them. Many observers have confirmed my conclusions; but the recent publication of Walker and Sellards'[13] experimental work on man with both cultural and parasitic amebas definitely proves every point for which I have contended for years. They have shown conclusively that the amebas that can be cultivated from water, from the feces of man and other animals and from other sources, are incapable, when ingested, of producing the symptoms or lesions of dysentery in man, and that they are not entamebas but free-living amebas, having nothing to do with the production of dysentery and unable to live as parasites in man. They have also proved beyond dispute that *E. histolytica* and *E. coli* are distinct species, and that when fed to man, *E. histolytica* produces the symptoms and lesions of amebic dysentery, while *E. coli,* though a parasitic species, is harmless.

While all of the essential points covered in this paper have been previously proved by experimentation on the lower animals, the results obtained by Walker and Sellards possess the very great advantage of having been worked out on man, the natural host of *histolytica* and *coli,* and, in my opinion, settle for all time the question of the relation of parasitic and cultural amebas to disease in man.

THE IMPORTANCE OF DIFFERENTIATING E. HISTOLYTICA AND E. COLI

In discussing the importance of differentiating between *E. histolytica* and *E. coli,* Walker[14] states that such differentiation is possible from a study of the morphology and life-cycle of these parasites, an opinion which I have constantly advocated, and which has been steadily gaining ground among students of the subject since the paper of Schaudinn first appeared, although some investigators, in their writings, have given the impression that such a differential diagnosis is a matter of the very greatest difficulty, only to be attempted by a protozoologist. While I would be the last to state that these parasites can be differentiated by one with little or no experience in the study of intestinal protozoa, I do believe that the study of a few suitable cases of infection should enable one to differentiate the common intestinal entamebas of man. Recent researches have shown that there are but two species of importance occurring in man and I am convinced that any one trained in the use of the microscope and in the study of the common bacteria and protozoa of man should have no difficulty in recognizing *E. histolytica* or *E. coli.*

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[13] Walker, E. L., and Sellards, A. W.: Philippine Jour. Sc., Sec. B, 1913, viii, 253.

[14] Walker, E. L.: Philippine Jour. Sc., Sec. B, 1911, vi, 259.

The importance of differentiating these parasites can hardly be overestimated, and attention was called to it in my first paper published in 1905. Our statistics regarding the occurrence of amebic dysentery are very largely valueless because but little effort has been made to identify the species of entameba present, numberless infections with *E. coli* being mistaken for infections with *E. histolytica* and diagnosed as amebic dysentery, whether symptoms were present or not. In fact, some practitioners have gone so far as actually to treat for amebic dysentery every person showing an ameba in the feces, even in the absence of any effort to identify the ameba present, and very wonderful records of successful treatment of this disease have been thus built up on mistaken diagnoses. The mere finding of an ameba in the feces means nothing unless the species be identified, and at present a diagnosis of entamebic dysentery based on anything else than the identification of the entameba present as *E. histolytica* is not only unscientific but unjustifiable.

It is now well known that *E. histolytica* may live in the intestine of man for weeks, or even months, before symptoms of its presence are noticed. Persons thus harboring the parasite are efficient "carriers" of the infection, and undoubtedly are largely responsible for the spread of the disease. The great importance of the recognition of such infections is evident, and to recognize them it is necessary to be able to differentiate this entameba from the harmless *E. coli,* so commonly present in most tropical and subtropical regions in healthy persons. The importance of the discovery of these "carriers" emphasizes the great value of a routine examination of the feces of people living in regions in which entamebic dysentery is endemic, even when no symptoms of intestinal disease are present, and may be compared with the importance of the examination of the blood of both healthy and diseased persons in malarial regions in the prophylaxis of that disease. Not only will the carriers of the infection thus be recognized, but treatment can be instituted when it will prove most efficient, that is, before severe lesions have been produced in the intestine.

The differential diagnosis of *E. histolytica* and *E. coli* depends on a careful study of the morphology and life-cycle of these parasites both in the living condition and in properly stained preparations. While I believe that one trained in the study of these organisms can differentiate them in the living condition, it is always best to confirm such a diagnosis by the study of a stained preparation. The methods given in the following section are those I have found most useful in my own work and all of them can be followed by anyone trained in laboratory technic. I have not endeavored to give a large number of methods of staining, as I have found that it is much better to perfect oneself in one or two methods rather than to try to master all that may have been recommended.

TECHNIC

The intestinal entamebas of man may be studied either in the living condition or in stained preparations, and with either method of examination a differential diagnosis between *E. histolytica* and *E. coli* can be made. The study of the living parasites has been sadly neglected by some protozoologists, largely because of lack of material, and I am firmly of the opinion that this neglect has led to many mistakes in the interpretation of vital phenomena because of the great reliance these authorities have placed on the morphology of the stained entamebas. Indeed, some investigators have gone so far as to state that these parasites should only be studied in stained preparations, a statement which appears absurd to one who has had the opportunity of studying many living preparations, for it is just as easy to differentiate these parasites in the living condition as when stained, if one has had sufficient experience.

While, as I have already stated, it is always well to confirm one's species diagnosis by stained specimens, I am satisfied that in most cases a diagnosis of *E. histolytica* or *E. coli* can be made without recourse to staining the organisms and that this is the best and simplest method of diagnosing all types of intestinal infection with entamebas.

Preparation of Living Specimens.—In examining feces for living entamebas a small portion of a freshly passed stool is picked up with a platinum loop, placed on a microscopic slide, covered with a cover-glass, and gentle pressure exercised until the material is evenly spread. Care should be taken not to make too thick a preparation and several should be examined before a negative result is reported. I have repeatedly found a few entamebas in the ninth or tenth preparation examined, and sometimes I have had to examine as many as fifteen preparations before entamebas were discovered.

The feces may be examined in the normal condition, that is, without previous purgation, or a purgative may be administered before the examination. In my own experience I have obtained the best results after the administration of a purgative, especially in the demonstration of infections with *E. coli*, but Walker[15] advocates the examination of stools without previous purgation, because of the greater ease with which a differential diagnosis between *E. histolytica* and *E. coli* may be made. This has not been my experience and I would recommend the administration of a saline cathartic before the examination in all cases in which the stools are well formed. If partially formed or formed stools are to be examined it is necessary to dilute a small portion of the feces with normal salt solution or the preparation will be too opaque for examination.

It is always best to examine the feces immediately after passage for in such specimens the vegetative stages of the parasites, if present, are motile and therefore easily recognized. Many authorities have stated that the diagnosis of an entamebic infection should never be made unless the entamebas are observed in a motile condition; but such advice is pernicious, in that it would result in overlooking all latent and chronic infections in which the entamebas are encysted and, of course, motionless. As the recognition of the latent cases or "carriers" is of the greatest practical importance from a prophylactic point of view, it can be easily understood that such a statement might result in great harm. As a matter of fact, to one who has had sufficient experience in the study of these parasites, it is just as easy to recognize a non-motile entameba as a motile one, provided degenerative changes have not occurred, and, as the cysts of entamebas persist unchanged for several hours in the feces, one may demonstrate them in material that has been collected for some time. In fact, in the tropics and subtropics, I have often observed motile entamebas in feces that had been kept at room temperature for several hours.

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[15] Walker, E. L.: (With Sellards) Philippine Jour. Sc., Sec. B, 1913, viii, 253.

If the feces are to be transported for any distance before the examination is made, they should be placed in a warm vacuum bottle or similar receptacle. No disinfectant should be mixed with stools that are to be examined for entamebas.

After preparing the specimen for examination as directed, the cover-glass should be ringed with petrolatum, and the specimen examined first with a $\frac{1}{6}$-inch objective and a 1-inch eye-piece, and later with the $\frac{1}{12}$-inch oil-immersion objective. If one is experienced in the examination of feces for entamebas much time will be saved by going over the specimen with the $\frac{2}{3}$-inch objective and 1-inch eye-piece, picking out the suspicious objects, and then examining them with the higher power objectives; but considerable experience is required to recognize the entamebas with the lower-power lens mentioned.

If the preparation contains motile entamebas, they are generally easily recognized even by one having little or no experience in the study of these organisms, but the non-motile, precystic and encysted forms, while very distinctive to an experienced observer, may be easily confused by the inexperienced with other bodies occurring in the feces. Attention to a few simple points, however, will serve to distinguish entamebas from other objects found in the feces. In the resting stage these parasites are larger than pus-cells or protozoa that could be confused with them, are more refractive in appearance, and are characterized by a nucleus which is small in size when compared with the nucleus of other cells, and which consists of a very refractive ring of minute granules enclosing a homogeneous substance. If blood is present in the feces the red blood-corpuscles are often observed within *E. histolytica* and this serves at once to distinguish this parasite from other cells or protozoa.

When the entamebas are encysted they are larger than the cysts of other intestinal protozoa, are spherical or oval in shape, very refractive, and possess a distinct cyst-wall. From two to eight or more nuclei are present within the cyst. It is comparatively easy to distinguish the cysts of *E. histolytica* from those of *E. coli*, as will be explained later.

The use of a warm stage or an incubator for holding the microscope is not necessary unless one desires to study the life-cycle of entamebas while living, when some apparatus that will keep the organisms at body temperature is absolutely necessary. Much may be learned regarding their vital activities from the study of living entamebas in this manner.

Preparation of Stained Specimens.—In structure the entamebas are very delicate organisms and it is undoubtedly true that any method of fixing and staining them will cause some distortion and morphological change, so that it is essential, if one desires the best results, to select staining methods that have been found to produce the least artificial change in the morphology of the parasites.

In 1905 I recommended[16] the use of Wright's stain, after dry fixation, as a useful clinical method of differentiating *E. histolytica* from *E. coli*, and my observations regarding the use of this modification of the Romanowsky stain have since been confirmed by James,[17] who has secured excellent results by double staining with Hastings' and Giemsa's stains. While these stains, however, preceded by dry fixation, will suffice for the differential diagnosis of these parasites, much better results, as regards morphological detail, are secured by wet fixation, followed by one of the hematoxylin stains, and as some of these methods are but little more difficult of application than the modifications of the Romanowsky stain, I believe that they should be generally adopted when stained preparations of the entamebas are to be studied.

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[16] 16. Craig, Charles E.: Am. Med., 1905, ix, 854, 897, 937.

[17] 17. James, W. M.: New York Med. Jour., 1913, xcvii, 702.

To prevent alteration in morphology at any stage of fixation or staining rapid handling and the use of the process of wet fixation are necessary, as drying markedly distorts the nuclear structure of the entamebas on which a considerable part of our differential diagnosis depends.

I believe that it is much better to make the smears of the material to be examined on microscopic slides, although some authorities prefer cover-glasses. The slides are easier to handle and a much larger smear may be made, thus increasing the chances of finding well-stained entamebas. Some form of jar should be used in which to place the various solutions used in the process of fixing and staining, to which the preparations are transferred during staining, and for this purpose I have found the Coplin staining-jar, which may be obtained from any dealer in microscopical goods, an excellent one.

The same directions should be followed in selecting material from the feces to be stained for entamebas as have been already described for making living preparations; but the smear must be made very rapidly and placed immediately in the fixing solution, to prevent drying, which, as remarked, will render it useless. The material may be smeared in various ways, but I have found that the simplest method is to place a small portion of the material to be examined near one end of the slide, and then to draw it forward over the slide with the end of another slide applied nearly at right angles to the slide containing the material. A little practice will be found necessary before thin, even smears are obtained, but the method is much better than rubbing the material over the slide with a platinum loop.

The character of the material examined has much to do with the success of smearing with a slide, for if much mucus be present it will be found impossible to spread it evenly in this manner, and then it will be necessary to use the platinum loop. If the feces are of solid consistence, an emulsion of a portion should be made with normal salt solution, and this emulsion used for making the smears. James recommends making the smears with a camel's-hair brush and this is an excellent method if little mucus is present. When the entamebas are few in the material to be examined, as determined by a preliminary microscopic examination, a portion may be diluted with warm normal salt solution, centrifuged, and smears then made from the sediment.

The most important points to bear in mind in making the smears are that they should be as thin as possible and that they should be placed in the fixing solution immediately.

Fixing the Preparations.—Many solutions have been recommended for fixing entamebas, but I have found that Schaudinn's sublimate-alcohol mixture answers every requirement and is a suitable mixture for use with any of the hematoxylin stains.

This mixture consists of two parts of a saturated solution of mercuric chlorid in normal salt solution, and one part of absolute alcohol. The mercuric chlorid solution is made by adding the mercury to boiling normal salt solution until saturation occurs. This may be kept indefinitely as a stock solution.

The mixture with the alcohol is made just before use and should be kept at the body temperature during the fixing process. The addition of 3 per cent. of glacial acetic acid improves the fixing qualities of the solution, but is not necessary.

Immediately after the smears are made they are immersed in this fixing fluid, which is heated to 37 C (98.6 F.), and fixed for five minutes. They are then transferred to jars containing various strengths of alcohol in the manner indicated in the following scheme:

In sublimate-alcohol, at 37 C. for five minutes; 50 per cent. alcohol for five minutes; again in 50 per cent. alcohol for five minutes; 70 per cent. alcohol for fifteen minutes; iodin alcohol (alcohol to which enough tincture of iodin has been added to produce a brown color) thirty minutes; 70 per cent. alcohol, until the yellow color given by the iodin disappears; 95 per cent. alcohol, thirty minutes; absolute alcohol, fifteen minutes; 80 per cent. alcohol, five minutes; 50 per cent. alcohol, ten minutes, and finally in distilled water, where they may be kept until stained.

The entire process should be carried out in staining-jars and only a few preparations handled at a time.

While the preceding process may seem complicated, it will not be found so in practice and the time consumed will be amply repaid by the excellent results obtained. The preparations must be carried rapidly from one solution to another as at no time must drying occur.

Staining the Preparations.—After the smears have remained in distilled water for ten minutes or longer they are ready for staining and the method selected will depend largely on the experience of the observer. I have found that the ferric chlorid hematoxylin stain of Mallory gives excellent results, and this is the method I would recommend for routine work. This stain and the method of applying it were first brought to my attention in the study of the entamebas by Dr. W. M. James of Ancon, and I have found both most valuable in the differentiation of *E. histolytica* and *E. coli.* In the following (Dr. James') method of staining, as in fixing, the greatest care must be taken that the smears do not dry at any stage of the staining process:

1. Having washed the preparations thoroughly in distilled water, place them on glass rods arranged over a large dish or jar, and pour over them a 10 per cent. aqueous solution of ferric chlorid, so that the preparation is flooded. This is the mordant and should be allowed to remain on the preparations for from ten to fifteen minutes.

2. Drain the preparations, one by one, and pour over them at once a 1 per cent. aqueous solution of hematoxylin, prepared by dissolving hematoxylin crystals in boiling distilled water until the mixture is cherry-red. The hematoxylin solution should be freshly prepared and just warm to the hand when used. As soon as the hematoxylin is added the mixture becomes black and the smear disappears from view; but enough hematoxylin should be added to render the smear just visible through the brownish-yellow solution covering it. The preparations are now allowed to stain for from five to ten minutes.

3. Wash the preparations thoroughly in distilled water by pouring a considerable amount over the smears or by placing them in at least two changes of distilled water contained in a staining-jar.

4. Decolorize in a 0.5 per cent. ferric chlorid solution, the decoloration being controlled by microscopic examination. When the majority of the entamebas show a well-defined nucleus having a distinct membrane and contaning chromatin granules, decoloration has reached the proper point and should be stopped. This is accomplished by washing in distilled water. If the preparations are very thick it will be necessary to use a 1 per cent. solution of ferric chlorid in decolorizing.

5. After decolorization, the preparations are rinsed in distilled water, washed in running tap-water for fifteen minutes, dehydrated in 95 per cent. and absolute alcohol, cleared in xylol, and mounted in acid-free xylol balsam. If desired, the preparations may be left in water for several hours, and they should remain in each of the alcohols for at least fifteen minutes.

While the preceding stain gives excellent results and is all that is necessary in routine work, more nearly perfect results, as regards the differentiation of nuclear structure, may be secured with the iron-hematoxylin method of Heidenhain. This method of enabling the morphology of protozoa to be studied has never been surpassed; but it requires considerable technical ability and experience before good results are obtained.

Two solutions are used in this method which is, in brief, the following:

Solution 1:

A 2.5 per cent. solution of iron alum. (Ferric ammonium sulphate.)

Solution 2:

Hematoxylin crystals	1 gm.
Absolute alcohol	10 gm.
Distilled water	90 gm.

The hematoxylin is dissolved by heat in the water and the alcohol added when the mixture is cold, after which it is placed in a dark glass bottle lightly corked with cotton, and allowed to ripen for a month or six weeks, at the end of which time it is tightly corked and ready for use.

Method of Using.—After fixing, as described, in sublimate-alcohol solution, the preparations are thoroughly washed in distilled water, and placed in Solution 1 for from eight to ten hours or over night; they are then rinsed in distilled water and placed in Solution 2, where they should remain for from twenty-four to forty-eight hours, after which they are rinsed, one by one, in distilled water, and placed again in Solution 1. When this is done dense black clouds come from the preparation but in from three to four minutes these almost disappear and only slightly blackish clouds are formed. When this point is reached the preparations should be washed in distilled water, and placed in a jar containing tap-water. The preparation should now be examined by mounting it in water with a cover-glass and using a high-power dry lens (a ⅙ or ⅛) and a 1-inch eyepiece. If the entamebas show a clearly defined nucleus containing chromatin granules, the decolorization has been sufficient, but if not, the preparation is again washed in distilled water, placed in Solution 1 for a second or two, then mounted with a cover-glass in Solution 1 and examined under the microscope. As soon as the entamebas show a well-defined nucleus, the specimen should be rinsed in distilled water, dehydrated for ten minutes each in 50, 70 and 80 per cent. alcohol, in 95 per cent. alcohol for fifteen minutes, and in absolute alcohol for twenty minutes; cleared in xylol and mounted in acid-free xylol balsam.

While the Heidenhain stain is most reliable in experienced hands, I am of the opinion that more mistakes have been made in the interpretation of the morphology of entamebas stained in this manner than with any other stain that has been used for this purpose. It is very easy to carry the process of decolorization too far, and to make the nucleus of *E. coli* resemble that of *E. histolytica* and I have repeatedly observed mistakes made by the best protozoologists in diagnosing between these species in preparations stained by the iron-hematoxylin method. For this reason the Heidenhain method is not so generally useful as the Mallory stain, for while some experience is required, even in the use of the latter stain, it is not so difficult to manipulate and, to secure good results, requires much less experience in its use.

It should be remembered, however, that no staining method is as useful in diagnosis as the examination of the living parasites, and while such methods are absolutely essential for the study of the minute morphology and reproductive cycle of the entamebas they are not essential either in the differentiation of *E. coli* and *E. histolytica* or in the clinical diagnosis of entamebic infection.

When entamebas are well stained, by either of the methods here mentioned, the cytoplasm is of a grayish color, while the nucleus is well defined, the nuclear membrane and chromatinic granules being stained a jet black. The entamebas may be confused, when stained, with other protozoa occurring in the feces or with animal or vegetable cells. It is seldom difficult for one who has had experience in the study of these parasites to differentiate them from other organisms or cells, and the cysts are very characteristic, by reason of their multiple nuclei. There are some vegetable cells having two or more nuclei that are often confusing to the inexperienced, being mistaken for the cysts of entamebas, but reference to the descriptions of the morphology of the true entamebic cysts should prevent such confusion. Certain protozoa, as *Trichomonas hominis, Lamblia intestinalis* and *Balantidium coli* might be confused with the intestinal entamebas at certain stages in their development, but such a mistake could be made only by one having a very superficial knowledge of protozoology. The *Blastocystis hominis*, a vegetable cell of uncertain origin, has frequently been mistaken for encysted entamebas, but differs greatly in morphology, only a small portion of the cell being occupied by the cytoplasm, which contains a few granules of material giving the staining reaction of chromatin.

A considerable number of pages might be written describing in detail the bodies of various kinds that may be confused with the intestinal entamebas, but only experience in this line of work will prevent mistakes, and this is better gained by the study of actual preparations than by reading about differential details.

THE DIFFERENTIAL DIAGNOSIS OF E. HISTOLYTICA AND E. COLI

The most recent observations on the intestinal entamebas have apparently proved that they pass through at least three distinct stages in their life-cycle when morphological changes occur of such importance that, unless one is well aware of them, grave errors may follow in their interpretation, and the species thus be confused. This has been proved by the number of years that elapsed before it was recognized that the so-called *E. tetragena* is actually but one stage in the development of *E. histolytica,* this being entirely due to false interpretation of the morphology and life-cycle of the parasite. The slavish insistence by some protozoologists on the absolute value of nuclear structure in the differentiation of the entamebas has been largely responsible for the mistakes that have been made in the study of these parasites, and it is questionable whether our knowledge has been advanced or delayed by the studies of the morphologists who have devoted their energies to the study of stained entamebas, instead of the living organisms.

When one remembers that slight variations in the technic of staining may cause the nucleus of *E. coli* to resemble so closely that of *E. histolytica* that the most expert protozoologists have been misled and have diagnosed one for the other, it will be easily understood how difficult it is for those having but a limited experience to differentiate species by the use of stained preparations.

The fact remains, that after over ten years of study of the intestinal entamebas by numerous protozoologists, we are now, so far as species are concerned, just about where we were immediately after the publication of Schaudinn's paper. While many new species have been described, and additions, important from a morphological point of view, have been made to our knowledge, we must admit that, at present, only two species of entameba have been actually proved to exist in the intestine of man, and these are the two species described by Schaudinn. We have heard, to adapt Omar:

> great argument
> About it and about: but, evermore,
> Came out by the same door as in we went.

It is true, however, that in properly stained preparations there are generally distinct differences in the appearance of the nucleus of *E. histolytica* and *E. coli,* that are sufficient to allow the experienced observer to distinguish them; while the cysts are quite characteristic for each species. Moreover, it is possible to differentiate them in the living condition, and this is undoubtedly the preferable method for the clinician. It should be understood that the morphology of these parasites varies greatly with the character of the feces containing them, and, therefore, with the clinical character of the infection, in the case of *E. histolytica.* The morphology of the latter species in cases of acute dysentery is quite different from that present in the subacute and chronic infections, so that it becomes necessary to describe the morphology of these parasites as related to the clinical course of the infection.

For convenience of description I shall consider the differentiation of *E. histolytica* and *E. coli* during the vegetative, precystic and cystic stages of development, in both living and stained preparations, indicating in the description the clinical character of the infection present at each stage of development, in the case of *E. histolytica.*

THE DIFFERENTIATION OF E. HISTOLYTICA AND E. COLI IN THE VEGETATIVE STAGE OF DEVELOPMENT

The morphology of these parasites varies greatly during the vegetative stage of development, being most typical when the feces are liquid in character, and, in the case of *E. histolytica,* when the most acute symptoms of dysentery are present. When the feces are semisolid in consistence, as in acute dysentery improving under appropriate treatment, the morphology of this species is that described for the vegetative stage of *tetragena* or the so-called precystic stage; while in the acute exacerbations that occur in chronic entamebic dysentery, the nucleus of *E. histolytica* is typical of the *tetragena* type of nucleus.

DIFFERENTIATION OF THE LIVING ENTAMEBAS

As I have stated, *E. histolytica* and *E. coli* may be distinguished in the living condition and this will be found the best method in ordinary practice.

Size.—It is impossible to differentiate the two species from the size of the organisms, for while *E. histolytica,* in the vegetative stage of development, is generally larger than *E. coli,* individuals of the latter species are observed that are fully as large as the average *histolytica,* and in the subacute types of dysentery *E. histolytica* may even average smaller than *E. coli.* It is when acute symptoms of dysentery are present that *E. histolytica* attains its largest size, measuring sometimes as much as 80 microns in the long diameter, when moving, but the average measurement is from 25 to 40 microns in diameter, when motionless. The measurement of *E. coli* is from 15 to 50 microns in diameter, but, as a rule, this species does not exceed 25 microns, although I have observed specimens measuring as much as 60 microns in diameter.

Shape.—*E. histolytica* is much more actively motile than *E. coli,* and, for this reason, varies more in shape when observed in freshly passed specimens of feces. While the latter is generally spherical or irregularly oval in shape, *E. histolytica* may be much elongated, finger-shaped, or very irregular, owing to its marked motility. Shape is of very little value, however, in the differentiation of the two species.

Motility.—In freshly voided feces *E. histolytica* is very actively motile when compared with *E. coli,* and this is a most valuable means of distinguishing them under the condition mentioned, for I have never observed a specimen of the latter species that approached in motility the commonly observed specimens of *E. histolytica.* In *histolytica,* motion is generally progressive in character, while in *coli* it often consists only in the sending out and withdrawal of pseudopodia unaccompanied by progressive motility. Even when progressive motion is observed in

E. coli it is sluggish in character, and very easily distinguished from the motion of *E. histolytica* when the two species are observed side by side. In my paper published in 1905[18] I called attention to the great value of motility in distinguishing between these two parasites, and in 1908[19] stated that "the motility alone will serve to distinguish these organisms, if both be observed in freshly voided feces; for it will invariably be found that the amebas exhibiting the most active form of motility will present morphological features which show that they belong to the pathogenic species." This opinion I still hold, and it is now held by most investigators who have carefully studied the living organisms.

Cytoplasm.—The cytoplasm of *E. histolytica* is divided into two well-defined portions, the ectoplasm and the endoplasm. The distinction between the two is most marked when the parasite is moving, the glass-like ectoplasm in the advancing pseudopodium being very clearly defined from the more granular and grayish endoplasm, but even in the motionless entameba there is frequently visible a narrow rim of clear ectoplasm. The ectoplasm is hyaline and glass-like in appearance while the endoplasm is granular or alveolar in structure and much less refractile. Vacuoles are often absent in organisms observed in freshly voided feces, but appear in the cytoplasm as the feces become cold. The clear, hyaline, homogeneous-appearing ectoplasm of this species is very characteristic and furnishes one of the most valuable differential features between it and *E. coli*, as they are observed in the living condition.

The cytoplasm in *E. coli* is also divided into an ectoplasm and endoplasm, but the two portions are poorly defined when compared with *E. histolytica.* The ectoplasm of *E. coli,* while distinguishable in the moving organism, does not present the clear glass-like appearance of that of *E. histolytica,* but approaches very closely to the endoplasm in appearance, and gradually merges with it, instead of presenting the well-marked line of demarcation between the two portions almost always observed in *histolytica.* In most instances the endoplasm of *E. coli* contains one or more vacuoles, although not infrequently specimens are observed that are free from vacuoles.

To one who has had considerable experience in the study of these parasites in the living condition, the differences in the appearance of the ectoplasm and endoplasm are alone sufficient to distinguish the two species.

Phagocytosis of Erythrocytes.—In my early papers[20] I called attention to the facts that *E. histolytica* was actively phagocytic for red blood-corpuscles, while *E. coli* was only rarely observed to contain them, and that this was a very valuable means of distinguishing the two species. This observation has been confirmed by almost every investigator who has studied these parasites in the living condition, and while the absence of erythrocytes from the cytoplasm of an entameba is of no diagnostic importance, their presence in any number in an entameba observed in feces is absolute proof that we are dealing with *E. histolytica.* In feces containing blood, specimens of *histolytica* are frequently observed containing erythrocytes, sometimes being absolutely filled with them, while in the same feces, specimens of *E. coli* are generally entirely free from erythrocytes, and, at most, contain but one or two. This fact is very useful in differentiating the species, and James, in an unpublished article, the manuscript of which he kindly sent me, says, regarding the phagocytosis of erythrocytes by these parasites:

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[18] Craig, Charles F.: Am. Med., 1905, ix, 854, 897, 937.

[19] Craig, Charles F.: Jour. Infect. Dis., 1908, v, 324.

[20] Craig, Charles F.: Am. Med., 1905, ix, 854, 897, 937; Internat. Clin., 1905, Series 14, iv, p. 242; Jour. Infect. Dis., 1908, v, 324.

> In mixed infections I have often observed erythrocytes in varying quantities in the interior of the pathogenic organisms, but I found them rarely within the coincident *E. coli*, and then only one or two at a time. Absence of erythrocytes from the endoplasm is not of any particular value in differentiation, but their presence in any quantity is a certain indication of a pathogenic species.

It will thus be seen that James, who has had an extensive experience in the study of these parasites on the Isthmus of Panama, confirms all that I have previously claimed regarding the importance of this phenomenon in the entameba. A good clinical rule to follow, therefore, is that an entameba occurring in a dysenteric stool and containing erythrocytes should be regarded as *E. histolytica.*

The Nucleus.—The characteristics of size, shape and division into ectoplasm and endoplasm are similar for *E. histolytica* as observed in the feces from acute dysentery cases and during the acute exacerbations in the chronic stage of the disease, but this is not true of the appearance of the nucleus, in either fresh or stained preparations. It was the nonrecognition of this fact that led to the description of the so-called *E. tetragena* as a new species, when, in reality, one stage in the development of *E. histolytica* was being observed. We now know that the nuclear structure of this species may vary, at various stages in the life-history, from that typical of *histolytica,* as described by Schaudinn, to that typical of *tetragena*, as described by Viereck and Hartmann, this variation being accompanied by definite changes in the clinical picture of infection with this species. When the disease is in the most acute stage, *E. histolytica* presents the typical *histolytica* type of nucleus, while in the subacute stage, and during the acute exacerbations of the infection in chronic cases, the *tetragena* type of nucleus is present. As the latter type of nucleus approaches that of *E. coli* morphologically, it is most important to differentiate it from the latter, and this is possible in stained preparations, but in living organisms the differentiation of the two species must be made on other features than the structure of the nucleus, when the *tetragena* type is present.

In acute cases of dysentery the nucleus of *E. histolytica* is usually invisible, and, when visible, consists only of a very delicate, refractile ring, representing the nuclear membrane, containing within it one or more refractile granules, representing the chromatin. In the vast majority of instances the nucleus of this species is invisible in cases presenting acute symptoms of dysentery, thus distinguishing it from *E. coli*, in which the nucleus is almost invariably visible in the living parasite.

The nucleus of *E. coli* consists of a well-defined ring of refractile granules, containing within it either scattered refractile granules, or a refractile mass near the center representing the karyosome. It is much larger than the nucleus of *E. histolytica* and can be seen with but little difficulty in either the motile or the immotile entamebas.

In *E. histolytica* the nucleus is generally situated near the periphery of the organism and changes its position rapidly with the movements of the ectoplasm or endoplasm, while in *E. coli* the nucleus is more central in position, and, owing to the slight motility of this species, it tends to remain stationary in the endoplasm.

In the subacute and early chronic cases of dysentery, however, when the nucleus of *E. histolytica* is of the *tetragena* type, it is also almost always visible, having a well-defined nuclear membrane consisting of a ring of refractile granules, while within it there is considerable chromatin in the form of refractile granules or masses. In my opinion, one would have to be very confident in his ability to differentiate minute morphology to assert that the nucleus of *E. histolytica* could be differentiated from that of *E. coli* in living organisms, when the *tetragena* type of nucleus is present. At this time the differentiation of the two species must rest on other data, as I have stated.

From what has been said it is evident that the differentiation of *E. histolytica* and *E. coli*, in the living condition and during the vegetative stage of existence, depends on several factors, the most important being motility, character of the ectoplasm and the endoplasm, and the phagocytosis of erythrocytes. In making such a differentiation I believe that any entameba occurring in the intestinal tract of man, possessing active motility of progressive character, having a well-differentiated ectoplasm and endoplasm, and containing erythrocytes, may unhesitatingly be diagnosed as *E. histolytica;* while an entameba having but sluggish motility, slight differentiation of the ectoplasm and endoplasm, and no erythrocytes in the endoplasm when the feces contain blood may be correctly regarded as *E. coli*. I myself would not hesitate to make a diagnosis of *E. histolytica* when the feces contain entamebas with erythrocytes within them, and I believe that this is a safe clinical rule to adopt.

DIFFERENTIATION IN STAINED PREPARATIONS

The differentiation of *E. histolytica* and *E. coli* in stained preparations, during the vegetative stage of development, depends entirely on the morphology of the nucleus and on the presence of erythrocytes within the cytoplasm. Neither shape nor the size, neither the presence or number of vacuoles nor the distinction between ectoplasm and endoplasm is of the least value in the differentiation of the species in preparations stained in the manner described in this contribution.

As in the living specimen, the presence of red blood-corpuscles within the endoplasm is sufficient to differentiate *E. histolytica* from *E. coli*, but very frequently the feces do not contain blood, and in such instances differentiation must depend entirely on the structure of the nucleus. This can be done, in properly stained preparations, by one experienced in the study of the protozoa, but, unless this is true, it is much more safe to rely on the differences in the morphology of the living parasites in differentiating the two species during the vegetative stage of life.

The Nucleus.—In wet-fixed and hematoxylin-stained preparations the nucleus of *E. histolytica* presents two distinct morphological types, the true *histolytica* type (Fig. 1), found in the most acute cases of dysentery, and the *tetragena* type (Fig. 2), found in the subacute or more chronic cases of the disease.

The *histolytica* type of nucleus, the species type, is spherical or oval in shape in the stained preparations, although if pressure has been used in making the smears the nucleus may be much distorted. It is characterized by the very delicate nuclear membrane, stained black, and often not more than a line in thickness. In some instances the membrane is thickened at one portion of the periphery, giving it a crescentic appearance. On the inner side of the nuclear membrane very minute dots of black-stained chromatin may sometimes be observed, while at the center of the nucleus there is a very minute and delicate karyosome, usually composed of a single dot or mass of chromatin. In rare instances a minute granule of chromatin, more deeply stained than the karyosome, may be seen lying within the latter, forming the centriole.

Within the nuclear plasma between the karyosome and the membrane a few minute dots of chromatin may be visible, lying on the nodal points of a faintly stained linin network, but very many organisms are observed in which the nucleus appears to consist only of a delicate nuclear membrane enclosing a minute karyosome, the hyaloplasm being entirely free from chromatin. At this stage of development the amount of nuclear

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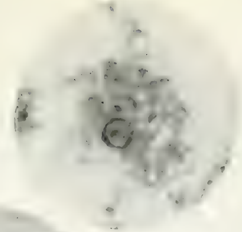

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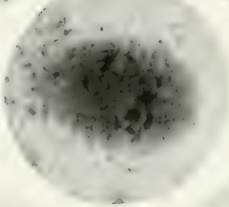

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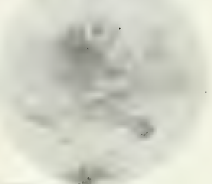

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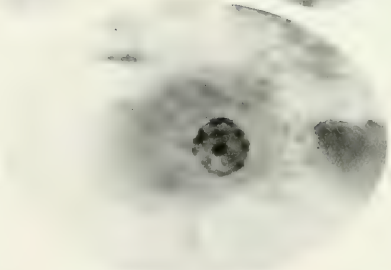

Fig. 1.—Vegetative form (trophozoite) of *E. histolytica*, showing typical *histolytica* type of nucleus; × 1.300. This and the following photomicrographs were taken with a No. 2 eye-piece and a 1⁄12 oil-immersion objective. All specimens were wet-fixed and stained with iron-hematoxylin. The photomicrographs were taken by Capt. Arthur C. Christy, Army Medical School, Washington, D. C., to whom my thanks are due for many courtesies.

Fig. 2.—Vegetative form of *E. histolytica* showing *tetragena* type of nucleus × 1.300.

Fig. 3.—Vegetative form of *E. histolytica* showing simple division. One nucleus is of the typical *histolytica* type, while the other is of the *tetragena* type; × 1.300.

Fig. 4.—Vegetative form of *E. histolytica*, in which the two nuclei resulting from division are of a modified *tetragena* type; × 1.300.

Fig. 5.—Vegetative form of *E. histolytica* undergoing simple division. The two nuclei are of the *tetragena* type; × 1.300.

Fig. 6.—Vegetative form of *E. coli*. Note clumps of chromatin on nuclear membane and the large compact karysome; × 1.200.

chromatin is much less in *E. histolytica* than in *E. coli,* while the nuclear membrane and karyosome are much more delicate in appearance.

In parasites undergoing simple division two nuclei may be observed, both of the *histolytica* type, although rarely one of the nuclei may be of the *tetragena* type, as shown in Figure 3. In the *histolytica* type of nucleus I have never observed the well-marked cyclical changes so characteristic of the *tetragena* type of nucleus.

The *tetragena* type of nucleus, which is characteristic of *E. histolytica* during certain stages of its development, differs so markedly from the *histolytica* type that for several years entamebas showing this type of nucleus were regarded as belonging to a distinct species. The nuclear membrane, in stained preparations, is of considerable thickness as compared with the membrane of the *histolytica* type and large clumps of chromatin are not infrequently observed on its inner surface. The chromatin may be collected at the center of the nucleus, forming a deeply stained, solid-appearing karyosome closely resembling that of *E. coli,* or more frequently, it has a characteristic arrangement within the nucleus, either being scattered on the inner side of the nuclear membrane or as minute, deeply stained granules on the dimly stained linin network, while the karyosome is comparatively large, irregular or roughly spherical in shape, surrounded by an unstained area, and containing a well-defined centriole. The latter consists of a deeply stained dot or mass of chromatin, sometimes also surrounded by an unstained area.

Certain well-defined cyclic changes, first described by Hartmann, occur in the nucleus of *E. histolytica* when the *tetragena* type of nucleus is present, and these changes are much more prominent in this species than in *E. coli.* The karyosome sometimes appears as a fine network enclosing an unstained area within which lies the centriole, which may show division into two granules; the outer border of the karyosome may be bounded by an unstained area of some extent, at the outer border of which the linin network is observed, the boundary of the clear unstained area being formed of distinct dots of chromatin circularly arranged. Again, the karyosome may stain almost uniformly throughout, the centriole appearing as a more deeply stained central dot, or it may be invisible. The linin network varies in staining qualities, at times being quite distinct while at others it is almost unstainable. Lying on the linin network there are generally numerous dots of chromatin which also vary in their arrangement, while the inner border of the nuclear membrane is covered with minute granules of chromatin, or irregular, larger masses, quite like those occurring commonly on the nuclear membrane of *E. coli.* These changes in the morphology of the nucleus of *E. histolytica* are certainly very characteristic of the species, for while somewhat similar changes also occur in the nucleus of *E. coli*, they are much less striking and offer no difficulty in the differentiation of the species.

In many instances, if one searches carefully, intermediate types of nuclei between the *histolytica* and *tetragena* types may be observed in *E. histolytica*, and organisms are observed containing two nuclei (Fig. 4). These parasites are undergoing simple division and the two nuclei may be of the *histolytica*, *tetragena* (Fig. 5) or intermediate type, or one may be of the *histolytica* type while the other is of the *tetragena* type, as already noted.

In stained specimens degenerative forms of *E. histolytica* are frequently observed, in which the nucleus has either wholly or partially disappeared and the cytoplasm contains threads, granules and blocks of chromatin. These are the forms that have been mistaken in the past for reproduction by gemmation or budding, and that have caused so much confusion in the differentiation of the species. In order to avoid such confusion it is a good working rule to regard any entameba showing chromidia within its cytoplasm as a degenerating organism which should not be considered in distinguishing between *E. histolytica* and *E. coli*.

The nucleus of *E. coli* differs from either the *histolytica* or *tetragena* type of nucleus of *E. histolytica* in being much richer in chromatin, having a thicker nuclear membrane, and a larger and more compact karyosome, in which cyclical changes are not so pronounced. While this is true of the vast majority of entamebas of this species, there do occur specimens of *coli* that have a nucleus very hard to distinguish from the nucleus of *E. histolytica*, when that nucleus is of the *tetragena* type, so that one should study several entamebas in every specimen of feces before arriving at a conclusion regarding the presence or absence of either species.

The nuclear membrane of *E. coli* is quite thick and stains an intense black with hematoxylin. It is even thicker than that of the *tetragena* type of *E. histolytica*, and presents on its inner surface granules or, more frequently, clumps of chromatin (Fig. 6). The karyosome most often appears as a deeply staining mass of chromatin, of comparatively large size, centrally situated within the nucleus, and containing no well-defined centriole. In some instances a centriole may be distinguished as a more deeply staining mass of chromatin near the center of the karyosome. In this species certain cyclical changes also occur in the nucleus and its appearance varies at different times; but they are not so evident as in the *tetragena* type of nucleus of *E. histolytica*. When there is a well-defined and large karyosome there is little evidence of a linin network or of chromatin within it or on the inner surface of the nuclear membrane, but when division of the karyosome occurs the linin network is clearly visible in well-stained specimens, contains much chromatin in the form of fine granules, and large clumps of chromatin may be observed on the inner side of the nuclear membrane (Fig. 6). The nucleus of *E. coli* is considerably larger than that of *E. histolytica*, in the vegetative stage of development, and, while it may at times resemble the latter in morphology, the thicker nuclear membrane, larger size (Fig. 15), more compact karyosome, and the larger masses of chromatin on the inner side of the nuclear membrane, should serve to distinguish it from any stage in the development of the nucleus of *E. histolytica*.

Specimens of *E. coli* are not infrequently observed undergoing simple division (Fig. 8), and in stained preparations it is possible to study this process from the initial division of the centriole to the complete division of the nucleus. Very frequently organisms are observed in which the karyosome consists of two deeply staining oval masses of chromatin situated near the center of the nucleus or near its periphery; others are observed in which the inner side of the nuclear membrane is covered with large, irregular clumps of chromatin, the karyosome having disappeared; and still others are observed containing two well-developed nuclei possessing the typical *coli* morphology, either situated side by side, or at some distance from one another.

Degenerative forms of this species also are frequent in stained preparations and may cause confusion; but a little study of them should be sufficient to lead to a correct diagnosis regarding their nature.

In summary, the following points are of most assistance in differentiating *E. histolytica* from *E. coli*, in stained preparations, during the vegetative stage of existence:

1. The delicate nuclear membrane and minute karyosome of *E. histolytica*, when the *histolytica* type of nucleus is present.

2. The presence of the loose karyosome, surrounded by an unstained area, and enclosing a well-defined centriole, characteristic of the nucleus of *E. histolytica*, when the *tetragena* type of nucleus is present.

3. The character of the chromatin observed on the inner side of the nuclear membrane in *E. histolytica*, the granules or clumps being smaller and less numerous than in *E. coli*.

4. The presence of erythrocytes within the cytoplasm, characteristic of *E. histolytica*.

The nucleus of *E. coli* is characterized, in stained preparations, by the thick nuclear membrane; the large, compact karyosome in which the centriole is either invisible or ill defined; and by the large clumps of chromatin frequently observed on the inner boundary of the nuclear membrane.

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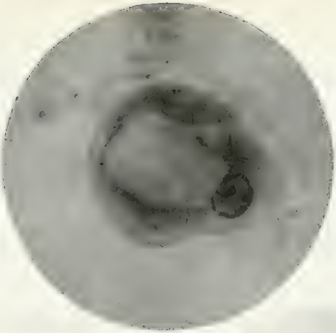

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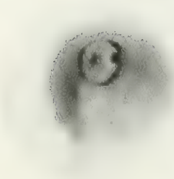

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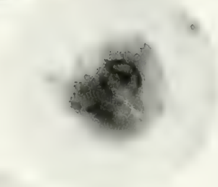

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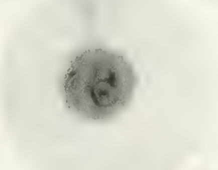

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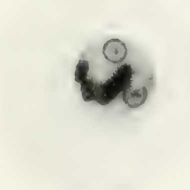

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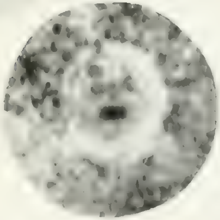

Fig. 7.—Very large cyst of *E. coli*, showing the large vacuole that is frequently present in the cysts before the primary division of the nucleus. Note the spindle-shaped karyosome which is frequently observed just prior to the division of this porton of the nucleus; × 1,200.

Fig. 8.—Young cysts of *E. coli*, showing division of the karyosome and the thick nuclear membrane; × 1,200.

Fig. 9.—Precystic form of *E. coli*. Note reduction in size and the elongation of the karyosome prior to division; × 1,200.

Fig. 10.—Early cystic stage of *E. histolytica*, showing small size and typical nucleus; × 1,150.

Fig. 11.—Encysted form of *E. histolytica*, showing the division of the primary nucleus into two nuclei; also the large chromidial masses characteristic of this species; × 1,150.

Fig. 12.—Encysted form of *E. histolytica*, showing the four daughter nuclei characteristic of the fully developed cyst; also a large chromidial body; × 1,150.

THE DIFFERENTIATION OF E. HISTOLYTICA AND E. COLI IN THE PRECYSTIC STAGE OF DEVELOPMENT

When the symptoms of dysentery are disappearing, that is, in subacute cases, there occurs a stage in the developmental cycle of *E. histolytica* in which the parasite becomes markedly reduced in size (Fig. 10) and the structure of the nucleus tends to assume a phase intermediate between that of the *histolytica* and *tetragena* types. This is the so-called precystic stage of the parasite and, as it occurs when symptoms are slight or practically absent, it is of importance that these entamebas be distinguished from the harmless *E. coli.* Unfortunately, it is just at this stage in their development that it is most difficult to differentiate the two species, and if only these forms be present it is often impossible. Enough typical vegetative or cystic forms are usually present, however, to enable one to make the diagnosis. In my opinion, it is this stage in the development of *E. histolytica* that has been described by Elmassian as *E. minuta.*

Living Preparations.—In the precystic stage of development *E. histolytica* is markedly reduced in size, the average measurement being from 10 to 20 microns in diameter; there is less distinction between the ectoplasm and endoplasm; motility is absent or very sluggish; and a nucleus is generally visible. It will thus be seen that at this stage of development this species is practically indistinguishable from *E. coli,* in the living condition. A careful search will generally reveal the presence of typical cysts or vegetative forms, however, but unless such are present, it must be confessed that it is mere guesswork, in the vast majority of instances, to state that *E. histolytica* is the parasite present.

Stained Preparations.—It is fully as difficult to differentiate the two species in the stained as in the living preparations, when they are in the precystic stage of development. At this time the nucleus of *E. histolytica* is morphologically intermediate in structure between that of the *histolytica* and *tetragena* type, the nuclear membrane being thickened, and the karyosome more compact and uniformly staining, while the centriole is often indistinguishable. All of these changes cause the nucleus of this species to resemble that of *E. coli,* there being a very considerable increase in the amount of nuclear chromatin preparatory to encystment. I believe that it is practically impossible, in the vast majority of instances, to differentiate the two species in stained preparations, at this time; but, as has been said, a careful search of the feces in such infections will generally show a few typical cysts or vegetative entamebas.

Very frequently the cytoplasm of both species contains chromidia in the form of threads, granules or clumps, and it is difficult to be sure whether such organisms are degenerating or whether the appearance of the chromidia is a normal process prior to cyst formation. These forms, however, may be disregarded as they are of no value in differentiating between the two species.

THE DIFFERENTIATION OF E. HISTOLYTICA AND E. COLI IN THE CYSTIC STAGE OF DEVELOPMENT

When the stools are semiformed or formed, following an attack of entamebic dysentery, or in the intervals between recurrences, *E. histolytica* undergoes encystment, the cyst containing four nuclei (Fig. 12) when fully developed. In formed stools *E. coli* also occurs in the encysted stage of development, the cyst of this species producing eight or more daughter nuclei (Fig. 13), eight being the normal number. As the cysts are the active agents of infection in both species, persons harboring them are efficient "carriers" of the infection, and hence the great importance of their discovery, especially in the prophylaxis of entamebic dysentery, which is caused by *E. histolytica.* Fortunately the cysts of *E. histolytica* and *E. coli* are quite easily recognized and differentiated both when living and when stained, and the routine examination of formed stools for these cysts in every person giving a history of diarrhea or dysentery should become as much a part of diagnostics as the examination of the sputum of persons giving a history of chronic cough. The following are the most characteristic features of the morphology of the cysts in both living and stained preparations.

Living Preparations.—The cysts of both species are spherical or oval in shape, refractive, and present a cyst wall which varies considerably in appearance with the age of the cyst, being delicate and single in outline in the younger cysts, and thicker and having a double outline in the older cysts.

Size.—The cyst of *E. histolytica* varies from 10 to 20 microns in diameter, the average being about 12 microns. The cysts of *E. coli* vary from 10 to 25 microns in diameter, the average being about 15 microns. It will thus be seen that the cysts of *coli* are considerably larger than those of *histolytica,* an important differential point.

Cyst Wall.—The cyst wall of both species, in the newly formed cysts, consists of a delicate membrane about a line in thickness, but in the older cysts the wall becomes much thicker, and generally has a double outline. The double outline is more distinct in the cysts of *E. coli* than in those of *E. histolytica*, but a differentiation of the species cannot be made from the character of the cyst wall.

Cytoplasm.—The appearance of the cytoplasm of the cysts of both species varies also with the age of the cyst. In the younger cysts the cytoplasm appears granular, and, in the case of *E. coli,* not infrequently contains included bodies, as bacteria and yeast-cells, but in the older cysts these have disappeared prior to nuclear division. In the early stages of nuclear division, before and directly after the primary division of the nucleus, a large vacuole may be present in the cytoplasm in both species, but afterward this vacuole disappears in the developing cysts.

Chromidia.—In the cysts of *E. histolytica* the cytoplasm very frequently contains brightly refractive, spindle-shaped, or irregular masses of chromatin, of large size, which are practically characteristic of the cysts of this species. While somewhat similar chromidial masses may rarely occur in the cysts of *E. coli,* I believe that it is justifiable to make a diagnosis of the presence of the cysts of *E. histolytica,* if these chromidial masses are present within the cyst. In the living organism they are very refractive and appear as shining masses within the cyst.

Nuclei.—The cysts of *E. histolytica,* when fully developed, are characterized by the presence of four nuclei. This number is never exceeded, in my experience, and any specimen of feces containing cysts containing no more than four nuclei may be considered as infected with this species. The nuclei appear as refractive, ring-like bodies within the cytoplasm, and it is generally necessary to focus up and down in order to bring them all into view, as they lie at different levels in the cyst. Any number of nuclei, up to and including four, may be seen in the cysts of *E. histolytica,* but never more than four.

The cysts of *E. coli* contain eight or more nuclei, when fully developed, the normal number being eight, but this is not infrequently exceeded, as cysts of this species may be observed that contain ten (Fig. 14), twelve, fourteen or even sixteen nuclei. The nuclei appear as refractive ring-like bodies, indistinguishable from those of *E. histolytica.* In my experience, any entamebic cyst occurring in the feces of man and containing more than four nuclei is the cyst of *E. coli.*

From the foregoing it is evident that in the living condition the cyst of *E. histolytica* may be distinguished from that of *E. coli* by its smaller size, the presence of the characteristic chromidial masses within the cytoplasm, and of from one to four nuclei. The cyst of *E. coli* is larger, has no chromidial masses, and may contain from one to sixteen nuclei, the normal number being eight.

Stained Preparations.—In the stained preparation, as in the living organism, the cyst of *E. histolytica* is smaller than that of *E. coli,* and the membrane is thinner and does not so often present a double outline. The characteristic differences, however, are the chromidial masses and the number of nuclei. The chromidial masses stain almost black and vary in number, only one or two being present generally. The nuclei stain intensely and are easily distinguished, but as they lie at different levels in the cysts it is necessary to focus carefully in order to be sure of the exact number. The number present, of course, determines the species of the cyst, the cysts of *E. histolytica* containing generally from two to four

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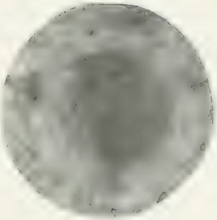

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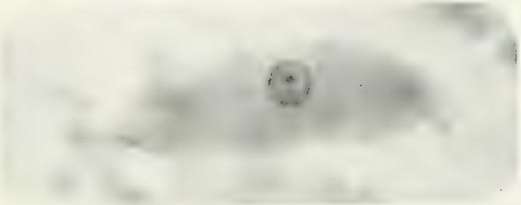

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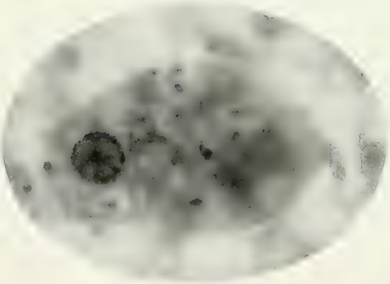

Fig. 13.—Cyst of *E. coli* containing eight nuclei. Only six are visible in the photomicrograph because two lay at a different level in the cytoplasm and thus are out of focus. Note size of cyst in comparison with cyst of *E. histolytica;* × 1,200.

Fig. 14.—Cyst of *Entameba coli* containing ten nuclei. Only five are visible, five being out of focus owing to their position in the cytoplasm. Note large size of cyst; × 1,200.

Fig. 15.—Vegetative form of *E. coli.* Note heavy nuclear membrane and large compact karysome; × 1,200.

Fig. 16.—Vegetative form of *E. coli.* Very large specimen showing typical nucleus; × 1,200.

nuclei, while those of *E. coli* generally contain from two to eight nuclei, this number being sometimes exceeded.

The structure of the nucleus as observed in stained preparations is quite similar, in each species, to that already described as characteristic, and, to one who has had much experience in the examination of these parasites, may alone be sufficient to differentiate the species, but this is best accomplished by attention to the number of nuclei present.

In almost every specimen examined cysts may be observed that are evidently undergoing degeneration, the cytoplasm containing numerous vacuoles and threads and granules of chromatin, while no nuclei are visible. These degenerate cysts have caused much confusion in the classification of entamebas, but are easily recognized and should not be considered in the differentiation of the two species under discussion. The normal cysts always contain well-stained nuclei and show no chromidia in their cytoplasm, with the exception of the large chromidial masses already described as characteristic of *E. histolytica.*

A tabular arrangement of the chief differential points between *E. histolytica* and *E. coli,* in both the living condition and in stained preparations as given below, may prove of service in the diagnosis of the species. It should be remembered, however, as I have stated elsewhere,[21] that "a differential diagnosis of these species does not rest on the presence of a single morphological feature, but should only be made after a careful consideration of all morphological data as well as the life-cycle of the organisms investigated." While this is true, it is also true that there are certain morphological characters that are actually specific, as the presence, in any number, of erythrocytes in the cytoplasm of *E. histolytica,* its four nucleated cyst, and the eight nucleated cyst of *E. coli.* When these are present it is an easy matter to distinguish the two species, but if only the precystic forms can be found, the differentiation is most difficult, requiring frequent examinations and the study of the life-cycle of the parasites.

IMPORTANT POINTS IN THE DIFFERENTIATION OF E. HISTOLYTICA AND E. COLI

VEGETATIVE STAGE OF DEVELOPMENT: LIVING PREPARATIONS

E. histolytica	*E. coli*
Actively motile.	Sluggishly motile.
Ectoplasm glass-like. Clearly differentiated from endoplasm.	Ectoplasm poorly differentiated from endoplasm. Not glass-like in appearance.
Nucleus often indistinct or invisible.	Nucleus visible and distinct.
Erythrocytes present in endoplasm when stools contain blood. Very characteristic.	Erythrocytes absent from endoplasm when stools contain blood.

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[21] Craig, Charles R.: The Parasitic Amebae of Man, Philadelphia, 1911, p. 195.

VEGETATIVE STAGE OF DEVELOPMENT: STAINED PREPARATIONS

Delicate nuclear membrane and minute karyosome, when *histolytica* type of nucleus is present.	Thick nuclear membrane and large compact karyosome (Fig. 15).
Well-defined karyosome surrounded by an unstained area and containing a centriole, when the *tetragena* type of nucleus is present.	Centriole generally invisible or indistinct.
Smaller granules and clumps of chromatin on inner side of nuclear membrane.	Large granules and clumps of chromatin on inner side of nuclear membrane (Fig. 16).
Cyclical changes very marked in the nucleus when the *tetragena* type is present.	Cyclical changes less marked in nucleus.
Erythrocytes present in endoplasm when stools contain blood.	Erythrocytes absent from endoplasm when stools contain blood.

PRECYSTIC STAGE OF DEVELOPMENT: LIVING AND STAINED PREPARATIONS

In both the living condition and in stained preparations the differentiation of *E. histolytica* and *E. coli* is most difficult in this stage of development, and often impossible. The diagnosis should rest on the character of the vegetative or cystic forms that are almost invariably present together with the precystic forms.

CYSTIC STAGE OF DEVELOPMENT: LIVING AND STAINED PREPARATIONS

E. histolytica	*E. coli*
Cyst smaller.	Cyst larger.
Cyst wall thin. Double outline less frequently observed.	Cyst wall thick. Double outline frequently observed.
Cyst contains characteristic chromidial bodies.	Cyst does not contain chromidial bodies.
Cyst contains from one to four nuclei; never over four.	Cyst contains from one to sixteen nuclei, the normal number being eight when the cyst is fully developed.

In conclusion I would urge the value of the study of the living parasites rather than stained preparations, in the differentiation of these two species of entamebas. I am convinced that for most clinicians this is the best and most practical method of distinguishing them, and that it is only those who have had a very limited experience in the study of the living entamebas who insist on the necessity of staining them in order to differentiate them. The data given in this paper are the result of the study of nearly twelve hundred cases of entamebic dysentery and of hundreds of infections with *E. coli*, and, in almost every case, I think it can be stated that the differentiation of *E. histolytica* and *E. coli* was first made on the living parasites without any special difficulty. In view of this experience I am greatly in favor of the study of living organisms rather than of stained preparations in attempting to distinguish the two species. There is one exception to this rule, and that is in the case of the cysts. I believe that the stained cysts are more readily differentiated than the living cysts, and in the search for "carriers" of these bodies better results will be obtained if stained preparations are made, as well as living preparations.

The differentiation of the harmless *Entameba coli* from the pathogenic *Entameba histolytica*, and the discovery of "carriers" of the latter species, are not academic questions, but are of the most vital importance in the diagnosis, treatment and prophylaxis of dysentery, and for this reason the microscopical examination of the feces, now so much neglected by the physician, should become a routine measure in the clinical study of every patient in regions where entamebic dysentery occurs.

STUDY XXI: THE IMMEDIATE EFFECT OF REPEATED DOSES OF THEOBROMIN SODIUM SALICYLATE AND THEOCIN ON RENAL FUNCTION IN ACUTE EXPERIMENTAL NEPHRITIS *

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BOSTON

Such authorities as Senator,[1] Osler,[2] Bradford,[3] Herrick[4] and Forschheimer[5] agree that in the treatment of acute nephritis a cautious trial with the use of diuretics may be made with safety, but that such drugs should not be given persistently unless a distinct effect is produced, since large doses or the continued effect of small doses may lead to scanty excretion of urine with retention of urinary products. The experimental evidence for this contention is slight.

Of the diuretics in clinical use, purin derivatives are given most extensively. The exact mechanism by which they produce diuresis is not altogether certain. Munk[6] and Schwartz,[7] from perfusion experiments on the isolated dog's kidney injected with caffein and allied drugs, found a marked diuresis without any evidence of increased flow of blood through the kidney, and concluded that these substances had a specific effect on renal secretory functions. Von Schroeder[8] and Loewi[9] confirmed these observations in normal animals, finding after injections of

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* Submitted for publication Jan. 16, 1914.

* This is one of a series of studies on experimental cardiorenal disease: Study I, Smith: Boston Med. and Surg. Jour., 1908, clviii, 696; Study II, Christian: Boston Med. and Surg. Jour., 1908, clix, 8; Study III, Christian: Jour. Am. Med. Assn., 1909, liii, 1792; Studies IV-XV, Christian, Smith and Walker: The Archives Int. Med., 1911, viii, 468-551; Study XVI, Christian and O'Hare: The Archives Int. Med., 1913, xi, 517; Studies XVII and XVIII, O'Hare: The Archives Int. Med., 1913, xii, 49, 61; Study XIX, Christian and O'Hare: Jour. Med. Research, 1913, xxviii, 227; Study XX, Walker and Dawson: The Archives Int. Med., 1913, xii, 171.

1. Senator: Nothnagel's Specielle Pathologie und Therapie, 1896, xix, (1), p. 64.
2. Osler: Practice of Medicine, 1909, p. 691.
3. Bradford: Allbutt and Rolleston's System of Medicine, 1908, iv, 607.
4. Herrick: Osler's Modern Medicine, 1908, vi, 143.
5. Forchheimer: Therapeusis of Internal Diseases, 1913, iv, 58.
6. Munk: Centralbl. f. die med. Wissensch., 1886, xxiv, 481.
7. Schwartz: Arch. f. exper. Path. u. Pharmakol., 1899, xliii, 1.
8. Von Schroeder: Arch. f. exper. Path. u. Pharmakol., 1887, xxii, 39.
9. Loewi: Arch. f. exper. path. u. Pharmakol., 1902, xlviii, 410.

caffein and other purin bodies an increased outflow of urine, salts and urea which they considered to be due to direct stimulation of the epithelium. Phillips and Bradford,[10] and Gottlieb and Magnus[11] supplemented these experiments by oncometer studies. They found usually after injection of diuretics of this group dilatation of the renal blood-vessels which was independent of changes in the aortic blood-pressure and which was accompanied by a marked diuresis; but occasionally diuresis occurred with little vascular dilatation or marked vascular dilatation without any additional outflow of urine. Therefore they believed that while the vasomotor phenomena were important in producing diuresis, more complex processes must be present to explain the effect of purin bodies. Fletcher, Henderson and Loewi[12] made parallel observations and drew identical conclusions. Frey,[13] however, using the oncometer, and Beco and Plumier,[14] working with a perfusion apparatus, found that the amount of urine following the injection of these diuretics was directly related to the quantity of blood going through the kidney in a given unit of time. Hence the evidence on the pharmacological action of the purin diuretics is conflicting. By the use of these drugs, however, in normal animals an increased outflow of urine and its solids occurs whether due to a specific dilating action on the blood-vessels of the kidney or to a stimulation of the renal epithelium or to a combination of both these effects.

Under pathological conditions the kidney's reaction to these drugs is varied. Hellin and Spiro[15] studied the action of caffein in rabbits poisoned with arsenic, aloin, chromium and cantharidin. Diuresis could be obtained in those nephritides in which tubular lesions predominated, but did not occur when the glomeruli were chiefly affected. Weber,[16] working on dogs, found that in chromium nephritis the kidneys were unable to excrete a concentrated urine, so that although sodium chlorid and theophyllin produced an increased outflow of fluid except in most advanced cases, yet there was no increase in the output of the solids of the urine, and in certain animals a retention. Hedinger attacked the problem from a different point of view. Schlayer and Hedinger,[17] and Schlayer and Takayasu[18] showed in experimental nephritis in rabbits that the renal vessels as tested in an oncometer were hypersensitive or hyposensitive to physiological stimuli at different stages of the disease.

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[10] Phillips and Bradford: Jour. Physiol., 1887, viii, 117.

[11] Gottlieb and Magnus: Arch. f. exper. Path. u. Pharmakol., 1901, xlv, 223.

[12] Fletcher, Henderson and Loewi: Arch. f. exper. Path. u. Pharmakol., 1905, liii, 15.

[13] Frey: Arch. f. d. ges. Physiol. (Pfluger's), 1906, cxv, 175.

[14] Beco and Plumier: Jour. de phys. et de path. gén., 1906, viii, 10.

[15] Hellin and Spiro: Arch. f. exper. Path. u. Pharmakol., 1896, xxxviii, 368.

[16] Weber: Arch. f. exper. Path. u. Pharmakol., 1906, liv, 1.

[17] Schlayer and Hedinger: Deutsch. Arch. f. klin. Med., 1907, xc, 1.

[18] Schlayer and Takayasu: Deutsch. Arch. f. klin. Med., 1910, xcviii, 17.

While hypersensitive the vessels dilated abnormally with a marked diuresis, while hyposensitive they no longer reacted and oliguria resulted. Hedinger[19] applied this method to animals injected with different renal irritants, using as vascular stimuli theophyllin, digalen and digipuratum in small doses. Diuresis occurred only when the renal vessels were physiologically intact. MacNider[20] was unable to confirm these results entirely. He observed the renal vascular response to caffein, theobromin, digitalen and saline solutions in dogs with uranium nephritis. His animals were divided into two main groups, those anuric or practically anuric with a normal blood-pressure and normal renal vascular system which showed no diuretic reaction to the various drugs, and those with an identical blood-pressure and renal vascular response which, however, had a definite diuresis. In the anuric group, the histological examination showed marked epithelial desquamation which produced an encroachment on the tubular lumen. In the second group this was less distinct. He concluded that mechanical obstruction to the lumen of the tubules played a part in determining the amount of urine. Mosenthal and Schlayer[21] studied the effect of repeated doses of sodium chlorid and caffein on the amount of urine and chlorid excretion and on renal volume as recorded by an oncometer in uranium and chromate nephritis in rabbits. In most advanced cases of each type of lesion neither diuretic was active; but in the early stage of chromate nephritis, sodium chlorid produced an increased outflow of urine and chlorid with renal dilatation, while caffein in repeated doses caused a diminishing amount of these substances with vascular contraction. In the early stage of uranium nephritis directly opposite results were obtained. These findings were explained on the assumption that in one type of lesion the functional condition was hypersensitive to fatigue by caffein, and in the other to fatigue by chlorid. Finally, Christian and O'Hare[22] gave theobromin sodium salicylate, and Walker and Dawson[23] gave theocin, caffein, potassium acetate and spartein sulphate from day to day to rabbits poisoned with uranium nitrate. In most severe cases all these drugs seemed to shorten the animals' lives, but in the less severe cases theobromin sodium salicylate, at least, apparently had a beneficial action. Therefore, from the literature it appears that in mild cases of acute experimental nephritis various diuretics cause an increased output of urine unless repeated rapidly enough to cause renal fatigue, and they are of possible therapeutic benefit. In severe cases, however, they are not pharmacologically active and are even injurious.

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19. Hedinger: Deutsch. Arch. f. klin. Med., 1910, c, 305.
20. MacNider: Jour. Pharm. and Exper. Therap., 1912, iii, 423.
21. Mosenthal and Schlayer: Deutsch. Arch. f. klin. Med., 1913, cxi, 217.
22. Christian and O'Hare: The Archives Int. Med., 1913, xi, 517.
23. Walker and Dawson: The Archives Int. Med., 1913, xii, 171.

Except for investigations regarding the total amount of urine and its constituents, no systematic studies have been reported as to the influence of diuretics on renal excretory functions under pathological conditions. This paper describes a series of experiments which were made to determine the immediate effect of repeated doses of theobromin sodium salicylate and theocin on the amount of water, nitrogen, sodium chlorid and phenolsulphonephthalein eliminated during different stages of acute experimental nephritis.

Rabbits were injected subcutaneously with toxic amounts of potassium bichromate or uranium nitrate in sufficient quantity to produce definite changes in renal function without rendering the animals anuric. These drugs were chosen because chromium produces marked tubular destruction in the kidney, leaving the glomeruli practically intact, while uranium nitrate produces lesions in both glomeruli and tubules. Thus renal function was tested under diverse pathological conditions. To obtain different degrees of severity of the same type of nephritis, animals were selected at varying times after injection and renal excretion was studied in the following manner: The animal to be observed was anesthetized by a subcutaneous injection of urethane (ethyl carbamate) in dosage of from 1.25 to 1.50 gm. per kilogram of body-weight. At the same time 2 gm. of urea and 2 gm. of sodium chlorid were administered in 50 c.c. of water by stomach-tube to insure a flow of salt and nitrogen containing fluid. It was realized that these three substances in themselves were powerful diuretics, but it was believed that after their rate of excretion was once established, any marked subsequent variation during the time of these experiments was due to changes in renal function brought about by the drugs introduced. Cannulas were inserted into the bladder and jugular vein according to the usual technic and the elimination of phenolsulphonephthalein, water, salt and nitrogen was followed.

The phenolsulphonephthalein test was slightly modified, but was made on the whole according to Rowntree and Geraghty's[24] method for obtaining constant output of the drug. At the beginning of the experiment, depending on the severity of the clinical condition of the animal, from 0.0015 to 0.006 gm. of the dye in 1 c.c. of saline solution was injected intravenously. After the color appeared, the urine during the next thirty minutes was measured in drops and diluted to 10 or 20 c.c. with distilled water, and the amount of phenolsulphonephthalein in an aliquot part estimated by Rowntree and Geraghty's modification of the Autenrieth-Königsberger colorimeter. Except when only traces were recovered, an amount of phenolsulphonephthalein equal to 10 per cent.

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[24] Rowntree and Geraghty: The Archives Int. Med., 1912, ix, 284.

more than the total amount recovered at this time was reinjected into the vein, to be excreted during the following interval, thus allowing for the loss between observations. In the few animals which were unable to excrete appreciable amounts of the drug, no further injections were made. In this way the phenolsulphonephthalein concentration in the blood and tissues was kept as nearly constant as possible, and any distinct increase or decrease in the excretion was assumed to be due to changes in renal function. At the end of every half hour the total amount of urine, nitrogen and salt excretion for the period was recorded. The nitrogen was quantitated by Kjeldahl's method, and the chlorids by the Lütke-Martius method. From these figures the concentration of nitrogen and salt in one hundred drops of urine was found. After the flow of water and phenolsulphonephthalein was approximately constant for two half-hour periods, theobromin sodium salicylate and theocin in increasing dosage were injected intravenously. As Hedinger[25] had found clinically that the repeated use of small amounts of diuretics often produces greater effect than single large doses, it seemed advisable to determine experimentally the action of repeated small injections of such drugs on renal function. Therefore, solutions of theobromin sodium salicylate[26] and theocin sodium acetate were made containing 10 mg. to the cubic centimeter of the former drug, and 5 mg. to the cubic centimeter of the latter drug (corresponding to 0.3 gm. of theobromin sodium salicylate and 0.15 gm. of theocin if given to a man weighing 150 pounds). At first 1 c.c. of theobromin sodium salicylate solution was given, followed in fifteen minutes by 2 c.c., yielding a total of 30 mg. of the drug. Then 1 c.c. of theocin solution was injected, and at fifteen-minute intervals 2 c.c., 3 c.c. and 4 c.c., making in all 50 mg. of the drug. Finally, the animal was killed and the kidneys were examined histologically after Zenker fixation and eosin-methylene blue staining. The drugs were given in this order and amount for arbitrary reasons. No effort was made to determine their relative efficacy of action. The experiments were conducted solely to discover the immediate effect on renal function in different kinds of acute experimental nephritis of the repeated injection of two typical purin diuretics.

The results have been grouped into three tables, each table representing the mean of eight experiments. While each observation in general showed the same features, by averaging them in this way, any exceptional finding due to individual peculiarity of the animal was ruled out.

Table 1 shows that under the conditions stated for the time observed, the excretion of fluid in normal animals diminished slightly but con-

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[25] Hedinger: München. med. Wchnschr., 1912, lix, 1098.

[26] The substance used in these experiments was the brand of theobromin sodium salicylate made by Knoll & Co., and sold under the proprietary name "Diuretin." The theocin sodium acetate was made by Bayer & Co.

TABLE 1.—Experiments on Normal Animals

PART I. NORMAL ANIMALS

Average of Rabbits I, II, III, 737:* Average weight, 1,750 gm. Histological findings negative. Urethane narcosis. At the beginning of the experiment each animal was given 2 gm. of urea and 2 gm. of sodium chlorid in 50 c.c. of water by stomach-tube. Injected intravenously with phenolsulphonephthalein.

Time Minutes from First Collected Urine	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
1–30	180	43	24	55	31	48	
35	...	..	..	..	..	..	Reinjected with phthalein.
35–65	175	54	31	48	27	46	
70	...	..	..	..	..	..	Reinjected with phthalein.
70–100	164	72	44	40	24	49	Killed.

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* The numbers of these animals correspond to those recorded in the laboratory of Theory and Practice, Harvard Medical School.

PART II. NORMAL ANIMALS WITH DIURETICS

Average of Rabbits III, IV, 731, 737: Average weight, 1,750 gm. Histological findings negative. Urethane narcosis. At the beginning of the experiment each animal was given 2 gm. of urea and 2 gm. of sodium chlorid in 50 c.c. of water by stomach-tube. Injected intravenously with phenolsulphonephthalein.

Time Minutes from First Collected Urine	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
1–30	96	47	49	45	46	52	
35	...	...	..	..	..	..	Reinjected with phthalein. 1 c.c. of theobromin sodium salicylate.
50	...	...	..	..	..	..	2 c.c. of theobromin sodium salicylate.
35–65	150	62	41	52	34	58	
70	...	...	..	..	..	..	Reinjected with phthalein. 1 c.c. of theocin solution.
85	...	...	..	..	..	..	2 c.c. of theocin solution.
70–100	584	198	34	70	12	66	
105	...	...	..	..	..	..	Reinjected with phthalein. 3 c.c. of theocin solution.
120	...	...	..	..	..	..	4 c.c. of theocin solution.
105–135	572	188	32	61	10	64	Killed.

TABLE 2.—Uranium Experiments

PART I. ANIMALS WITHOUT DIREUTICS

erage of Rabbit 754: 5 mg. of uranium nitrate subcutaneously; 48-hour nephritis histologically showing marked tubular lesions.

erage of Rabbit 755: 3 mg. of uranium nitrate subcutaneously; 24-hour nephritis histologically showing mild tubular lesions.

erage of Rabbit 756: 5 mg. of uranium nitrate subcutaneously; 72-hour nephritis histologically showing mild tubular lesions.

erage of Rabbit 757: 6 mg. of uranium nitrate subcutaneously in divided doses; 48-hour nephritis histologically showing advanced tubular lesions and slight glomerular lesions.

Average weight, 2,000 gm. Urethane narcosis. At the beginning of the experiment each animal s given 2 gm. of urea and 2 gm. of sodium chlorid in 50 c.c. of water by stomach-tube. Injected travenously with phenolsulphonephthalein.

Time Minutes rom First Collected Urine	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
1–30	213	59	28	30	14	21	
35	...	...	..	..	..	..	Reinjected with phthalein.
35–65	184	44	24	32	17	21	
70	...	..	..	..	..	..	Reinjected with phthalein.
70–100	137	29	21	27	20	18	
105	...	..	..	..	..	..	Reinjected with phthalein.
105–135	138	23	17	25	18	20	Killed.

PART II. ANIMALS WITH DIURETICS

verage of Rabbit 741: 3.5 mg. of uranium nitrate subcutaneously; 24-hour nephritis histologically showing mild tubular lesions.

verage of Rabbit 730: 9 mg. of uranium nitrate subcutaneously in divided doses; 120-hour nephritis, histologically showing advanced tubular lesions, and slight glomerular lesions.

verage of Rabbit 728: 4 mg. of uranium nitrate subcutaneously; 48-hour nephritis histologically showing marked tubular lesions.

verage of Rabbit 729: 5 mg. of uranium nitrate subcutaneously in divided doses; 96-hour nephritis, histologically showing marked tubular lesions.

Average weight 1,900 gm. Urethane narcosis. At the beginning of the experiment each animal as given 2 gm. of urea and 2 gm. of sodium chlorid in 50 c.c. of water by stomach-tube. Injected ntravenously with phenolsulphonephthalein.

Time Minutes from First Collected Urine	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
1–30	176	68	39	18	10	16	
35	...	...	..	..	..	..	Reinjected with phthalein. 1 c.c. of theobromin sodium salicylate solution.
50	..	...	..	..	..	..	2 c.c. of theobromin sodium salicylate solution.
35–65	332	91	28	32	10	17	
70	..	...	..	..	..	..	Reinjected with phthalein. 1 c.c. of theocin solution.
85	..	..	..	..	..	..	2 c.c. of theocin solution.
70–100	496	137	28	38	07	18	
105		...	..		..	..	Reinjected with phthalein. 3 c.c. of theocin solution.
120	...	...		..	..	..	4 c.c. of theocin solution.
105–135	369	97	26	39	11	18	Killed.

stantly, while chlorid and nitrogen excretion varied somewhat both in amount and in concentration without bearing direct relation to the amount of urine. The phenolsulphonephthalein excretion remained almost unchanged. When the diuretics were injected there was a pronounced increase in the amount of urine passed, paralleled by that of sodium chlorid. The concentration of chlorid became lower, suggesting that the excess of salt was carried through the kidney by water. The output of nitrogen was less affected by the diuresis, but increased as did that of the phenolsulphonephthalein, agreeing with Rowntree and Geraghty's[24] observations. On the whole, in normal animals the immediate effect on renal function of repeated injections of theobromin sodium salicylate and theocin was beneficial. This was shown by an increased output of water, chlorid, nitrogen and phenolsulphonephthalein; but by repeated dosage there was evidence of beginning renal fatigue, since the excretion of all these substances diminished during the last period of observation.

As in the first part of Table 1, animals with uranium nephritis which had not received diuretics (Table 2) showed a constant diminution in the amount of urine. In this series the chlorid and nitrogen decreased both in amount and in concentration. The phenolsulphonephthalein remained unchanged. The theobromin sodium salicylate and theocin produced a definite reaction. There was a marked increase in the amount of urine paralleled by that of nitrogen and chlorid without any increase in concentration. The amount of phenolsulphonephthalein, however, did not vary to an appreciable degree. In the last period the evidence of renal fatigue was exaggerated. The total amount of urine and salt diminished to a greater extent than in normal animals, though remaining above the initial level, while the nitrogen and phenolsulphonephthalein were unaffected. Therefore, in uranium animals the immediate effect on renal function of repeated injections of theobromin sodium salicylate and theocin was not harmful. There was an increased output of water, chlorid and nitrogen with an unchanged excretion of phenolsulphonephthalein. The kidney was fatigued more easily than under normal conditions, as shown by the diminishing output of salt and water under the influence of repeated injections of the drugs.

Table 3 shows the effect on animals poisoned with potasium bichromate and treated in similar fashion. As in the previous control experiments, animals without diuretics showed a constant falling off in their salt and water excretions, although the excretion of nitrogen increased without relation to the total amount of urine. The elimination of phenolsulphonephthalein was nearly constant. The action of the diuretics was less marked. While both salt and water were excreted in increased amounts they were proportionately less well put out than in the previous

TABLE 3.—Bichromate Experiments

PART I. ANIMALS WITHOUT DIURETICS

Average of Rabbit 762: 20 mg. of potassium bichromate subcutaneously; 72-hour nephritis histologically showing mild tubular lesions.

Average of Rabbit 763: 20 mg. of potassium bichromate subcutaneously; 72-hour nephritis histologically showing mild tubular lesions.

Average of Rabbit 764: 40 mg. of potassium bichromate subcutaneously; 96-hour nephritis histologically showing mild tubular lesions.

Average of Rabbit 765: 40 mg. of potassium bichromate subcutaneously; 96-hour nephritis histologically showing well-marked tubular lesions.

Average weight 2,500 gm. Urethane narcosis. At the beginning of the experiment each animal was given 2 gm. of urea and 2 gm. of sodium chlorid in 50 c.c. of water by stomach-tube. Injected intravenously with phenolsulphonephthalein.

Time Minutes from First Collected Urine	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
1–30	221	56	25	35	16	45	
35	...	..	..	..	..	..	Reinjected with phthalein.
35–65	219	64	29	38	17	45	
70	...	..	..	..	..	..	Reinjected with phthalein.
70–100	180	54	30	40	22	43	
105	...	..	..	..	..	..	Reinjected with phthalein.*
105–135	180	49	27	41	23	40*	Killed.

* Represents average of three animals. In one animal part of injection was lost.

PART II. ANIMALS WITH DIURETICS

Average of rabbit 732: 20 mg. of potassium bichromate subcutaneously; 24-hour nephritis histologically showing mild tubular lesions.

Average of rabbit 734: 20 mg. of potassium bichromate subcutaneously; 72-hour nephritis histologically showing no lesions, but functionally abnormal.

Average of rabbit 735: 20 mg. of potassium bichromate subcutaneously; 96-hour nephritis histologically showing marked tubular lesions.

Average of rabbit 743: 20 mg. of potassium bichromate subcutaneously; 24-hour nephritis histologically showing mild tubular lesions.

Average weight 1,800 gm. Urethane narcosis. At the beginning of the experiment each animal was given 2 gm. of urea and 2 gm. of sodium chlorid in 50 c.c. of water by stomach-tube. Injected intravenously with phenolsulphonephthalein.

Time Minutes from First Collected Urine	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
1–30	192	64	33	40	21	33	
35	...	..	..	..	..	..	Reinjected with phthalein. 1 c.c. of theobromin sodium salicylate solution.
50	...	..	..	..	..	..	2 c.c. of theobromin sodium salicylate solution.
35–65	224	57	25	40	18	28	
70	...	..	..	..	..	..	Reinjected with phthalein. 1 c.c. of theocin solution.
85	...	..	..	..	..	..	2 c.c. of theocin solution.
70–100	351	96	27	45	13	24	
105	...	..	..	..	..	..	Reinjected with phthalein. 3 c.c. of theocin solution.
120	...	..	..	..	..	..	4 c.c. of theocin solution.
105–135	260	64	25	30	11	18	Killed.

series. There was no definite increase in nitrogen excretion, and during the last period a diminution. The most striking feature, however, was the steady decrease in phenolsulphonephthalein elimination during the entire time of observation. In chromate nephritis, therefore, the immediate effect of purin diuretics was to produce a slight diuresis of water and salt, to have little effect on the excretion of nitrogen and to hinder that of phenolsulphonephthalein. If a large enough amount of drugs were given, the kidney was more easily fatigued than in normal or uranium animals, as shown by a greater lessening in the excretion of all the substances studied.

In addition a series of experiments with cantharidin nephritis was attempted. When sufficient amount of the poison was given to produce outspoken lesions, it was found that the animals became anuric and failed to react to the diuretics, confirming the observations of Hellin and Spiro,[15] Schlayer and Hedinger[17] and Schlayer and Takayasu.[18] If lesser amounts were injected, the anatomical and functional conditions of the kidney were so little changed as to make the observations of no value. These experiments, therefore, have been discarded.

On the whole, in normal animals the immediate effect of injections of theobromin sodium salicylate and theocin was to produce an increased outflow of urine, sodium chlorid and to a less extent of nitrogen and phenolsulphonephthalein. After repeated small doses of the drug were given the kidney became fatigued and excreted these substances in lesser amounts.

In animals suffering from uranium nephritis of varying intensity a similar immediate response to these diuretics was obtained except that the kidney became more easily fatigued. In chromium nephritis, on the other hand, while the kidney responded to the theobromin sodium salicylate and theocin by increasing the output of water and chlorid, yet the excretion of nitrogen remained almost constant and that of phenolsulphonephthalein diminished. After large amounts of the drugs had been injected, the signs of renal fatigue were more pronounced than in uranium nephritis or normal animals as the water, chlorid, nitrogen and phenolsulphonephthalein excretions diminished with greater rapidity.

Mosenthal and Schlayer[21] have demonstrated differences in renal fatigability to repeated injections of caffein and sodium chlorid in uranium and chromate nephritis. In these experiments following repeated injections of purin diuretics the kidneys became more easily fatigued in relation to excretion of the substances studied in chromate nephritis than in uranium nephritis or normally. Thus these observations are to a certain extent confirmatory of previous work.

Folin, Karsner and Denis[27] have shown that the non-protein nitrogen of the blood of animals having acute toxic nephritis accumulated in proportion to the severity of the disease. It was most pronounced in uranium and cantharidin nephritis and least marked in chromate nephritis. Clinically, it has long been recognized as a grave prognostic sign in kidney disease. Frothingham, Fitz, Folin and Denis,[28] working with rabbits poisoned with uranium nitrate, showed that the curve of nitrogen accumulation in the blood and of the excretion of phenolsulphonephthalein in the urine correspond closely. Therefore, it seems reasonable to conclude that in uranium nephritis the immediate effect of theobromin sodium salicylate and theocin was beneficial, for by the use of these drugs the outflow of water, sodium chlorid and nitrogen was increased, thereby tending to prevent nitrogenous accumulation in the blood. In chromate nephritis, however, the immediate effect of these diuretics was harmful, since, although they increased the outflow of water and chlorid, the nitrogen excretion was unaffected and the phenolsulphonephthalein elimination was diminished. In each nephritis repeated injections of theobromin sodium salicylate and theocin to the point of fatigue of the kidney was harmful to the renal function by producing a diminution in the total amount of urine, chlorid, and to a less degree, of phenolsulphonephthalein and nitrogen excreted.

CONCLUSIONS

1. The immediate effect of repeated small doses of theobromin sodium salicylate and theocin on renal function in acute experimental uranium nephritis of different degrees of severity is beneficial since they cause an increased output of urine, chlorid and nitrogen and do not diminish the excretion of phenolsulphonephthalein.

2. The immediate effect of repeated small doses of theobromin sodium salicylate and theocin on renal function in acute experimental bichromate nephritis of different degrees of intensity is harmful, since although an increased output of urine and chlorid occurs, the excretion of nitrogen is unaffected and that of phenolsulphonephthalein is diminished.

3. The repeated injection of small doses of theobromin sodium salicylate and theocin in sufficient amount produces a condition of renal fatigue in which the kidney is no longer able to react. This is most easily obtained in bichromate nephritis.

4. Various types of acute experimental nephritis respond differently to repeated injections of theobromin sodium salicylate and theocin both in regard to immediate changes in the excretion of chlorid, nitrogen and

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[27] Folin, Karsner and Denis: Jour. Exper. Med., 1912, xvi, 789.

[28] Frothingham, Fitz, Folin and Denis: THE ARCHIVES INT. MED., 1913, xii, 245.

phenolsulphonephthalein and in regard to the degree of renal fatigue which is induced.

5. These experiments do not include observations on nephritis of the most extreme grade of severity. In the few studies made on animals which had the different kinds of lesions and were anuric, the diuretics were not active in provoking an increased output of either water, chlorid, nitrogen or phenolsulphonephthalein.

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THREE CASES OF ADAMS-STOKES SYNDROME WITH HISTOLOGICAL FINDINGS [*]

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Although it is established that a complete transverse lesion of the stem of the auriculoventricular conducting system or of its two main branches results in auriculoventricular dissociation, and although a few years ago the problem of heart-block seemed almost settled by the discovery of lesions in the conducting system, it is now apparent that the solution of this problem is not so simple as it appeared at that time. There are cases on record in which heart-block was proved beyond a doubt, but still no lesions in the hearts adequately explaining the failure of the conduction of impulses from auricle to ventricle were to be found.[†]

The three cases to be presented show three very different histological conditions in the conducting system; and it is somewhat unfortunate that the clinical data do not give us such definite information of the mechanism of the heart as can be positively correlated with these post-mortem findings.

Three hearts from patients with a clinical history suggesting heart-block were kindly entrusted to us for microscopic examination; two by Dr. MacCallum and one by Dr. Bishop.

HEART 1.—*Case Report.*—The case report has been given by Dr. Bishop.[1] The patient, a watchman, aged 75, was admitted to Lincoln Hospital, Oct. 22, 1908. His family history was negative. He had had measles, whooping-cough and small-pox when a child. Later in life he had had muscular rheumatism and a sunstroke. He had drunk whisky moderately. Syphilitic history was denied. The patient was described as having a slow pulse, vertiginous and syncopal attacks and rapid venous pulse. The radial artery was not thickened, even to the degree that would be expected in a patient of his age. A polygraphic tracing was published in the original article.

Macroscopic Examination of the Heart.—The post-mortem examination of the heart was made by Dr. Larkin.[2] "The heart showed a calcareous nodule, situated precisely in the path of the bundle of His. This nodule was evidently the cause of the complete heart-block observed during life."

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[*] From the Pathological Laboratory of Columbia University, at the College of Physicians and Surgeons, New York City; read in abstract before the New York Pathological Society, Nov. 12, 1913.

[†] A. F. Stanley Kent has described in detail another connection between the auricle and ventricle beside the bundle of His, situate at the right lateral border of the human heart. (Proc. Roy. Soc., London, 1914, Series B., lxxxvii, No. B594, Biological Sciences, p. 198.)

[1] Bishop: Am. Jour. Med. Sc., 1910, cxxxix, 62.

[2] Bishop and Larkin: Proc. New York Path. Soc., 1909, New Series IX, 58.

The heart was received from Dr. Bishop in formaldehyd solution and the measurements of the preserved heart revealed nothing of interest.

The edges of both mitral cusps were shrunken and deformed and one could feel a hard calcareous deposit all along the attachment of the posterior cusp. The aortic cusp of the mitral valve was thickened throughout and contained irregular, rough, hard calcareous deposits. This calcareous mass was continuous with that described above in the upper portion of the interventricular septum and in the space between the anterior and right posterior cusps of the aortic valve, that is, directly in the normal pathway of the bundle of His. The cusps of the aortic valve were markedly thickened. The wall of the aorta itself showed patches of atheroma. The coronary arteries, both right and left, presented a very marked sclerosis with patches of atheroma.

Microscopic Examination.—Such a portion of the heart was removed for microscopic examination as would include the calcareous mass which seemed macroscopically to be situated precisely in the path of the bundle of His; namely, such a portion of the septum between the two halves of the heart as included the node, stem, and the branching of the auriculoventricular system. The upper margin of this block ran along the upper edges of the aortic leaflets, and the lower margin parallel with this 3 cm. below the lowest part of the pars membranacea septi.

This piece of tissue was decalcified with nitric acid, embedded in paraffin, cut from above down, parallel with the upper margin, in sections 15 to 19 microns thick. Altogether 2520 sections were cut and for a preliminary study every fortieth mounted. Finally about every fourth section from Section 1322 (where the node was first seen) to 1618 (well beyond the break in the continuity of the auriculoventricular system), and about every tenth from 1618 to 2440, was mounted. All the sections were stained with Weigert's iron hematoxylin and van Gieson's picric acid fuchsin solution except Sections 1392, which was stained with hematoxylin and eosin, and 1334, which was stained by Roehl's method for calcium.

The auriculonodal connections are attenuated (especially the strand to the left) but are uninterrupted. A very few round cells and still fewer polymorphonuclear cells are found at this junction and in the node itself.

The node lies, as usual, to the right of the central fibrous body, but is peculiar in that it is largely cut off from the auricular musculature by fatty tissue. It consists of a network of pale, fine muscle-fibers with crowded nuclei. The nodal artery shows increase of connective tissue in the intima and media; indeed there is sclerosis of the vessels throughout the whole of all the sections.

The node and stem are continuous. The stem is characterized by a greater vascularity, a more marked cellular infiltration and by the presence of more connective tissue than the node, which characters are so marked in the auriculoventricular system at and near the bifurcation of the stem as undoubtedly to be beyond normal limits. The stem progresses normally through the membranous septum in a short course and comes to lie under the endocardium of the left ventricle, when abruptly at its forward end it abuts on a calcified necrotic sphere there bifurcating to form what were judged to be stumps of the right and left branches. The calcified sphere, which lies directly across the path of the stem at its bifurcation, stretches from the endocardium of the left ventricle almost to that of the right.

This calcified sphere forms part of an area of calcification which begins just below the anterior aortic (coronary) cusp and involves the stump of the mitral valve, the connective tissue of the auriculoventricular ring and the undefended space, and the surrounding musculature, namely, that of the left auricle and of the basal part of the interventricular septum and of the auriculoventricular bundle. The area consists in the main of nodules of calcified necrotic material well encapsulated by connective tissue sheaths. In and immediately about some of the encapsulated nodules there is increased vascularity accompanied by pus cells (mostly round cells but not a few polymorphonuclears). There is also here and there the typical invasion of the calcific nodules by young connective tissue with an occasional giant cell.

At one level, one of these calcific nodules appears to the right of the ventricular end of the stem abutting on its narrowest part, and comes to lie in an indentation of the stem giving the appearance of compressing it. This occurs not far from the bifurcation, namely, at the forward end of the stem, which is composed mostly of thin-walled engorged blood-vessels and connective tissue and proportionately very few muscle-fibers. The undoubted increase in connective-tissue elements and vascularization which characterizes the ventricular portion of the stem also exists in the stumps of the right and left branches.

The stumps just mentioned are, judging by their position, probably the true branches and not the result of a mere splitting of the stem owing to pathological conditions. The lesion in this angle is, as has already been mentioned, a large calcific necrotic sphere which separates the stem and stumps from the rest of the right and left branches proper (Figure 1). The left branch proper is easily identified, but the identification of the continuation of the right branch we cannot assert with the same conviction.

Even on a naked-eye study of the sections it is clear that as one goes from the aortic valve toward the apex of the heart the calcific, necrotic focus involves a more and more extensive area and compromises the auriculoventricular system more and more. And microscopic study reveals that in Section 1462 there is no viable muscle-fiber in the stump of the right branch and that in Section 1480 there is not even an indication of the stump of the right branch,[3] that in Section 1502 there are no muscle-fibers in the stump of the left branch, and that there is in the region of Section 1544 from above down a hiatus of about 1 mm. (1.026 mm.) in the stem where there is no viable musculature. At this level the stem region consists of vascularized connective tissue with much cellular infiltration (mostly round cells, an occasional polynuclear, and a few cells larger than round cells characterized by more cytoplasm and a less compact nucleus).

To summarize, there are for a short distance (examining from above down) no muscle-fibers in the stem. Above this hiatus a large calcific necrotic sphere intervenes between the stem at its bifurcation on the one hand and the right and left branches on the other, and it is only below this hiatus that one branch (namely, the left) is continuous with the body of the stem. In brief, the right and left branches are cut off from the auriculonodal junction because necrotic tissue is situated in the path of the auriculoventricular bundle.

The two branches, cut off as they are from the node, present no abnormalities in their structure.

It should be borne in mind that the identification of the "main" part of the right branch as it descends downward is not absolute, since it is nowhere continuous with the stem, and was judged by its location, the lack of density of its muscle-fibers and its isolation. Farther up, the muscle-fibers of the right limb are slightly finer than those of the surrounding musculature, farther down, slightly coarser with occasionally a clear central space. At one level a small group of muscle-fibers which lies between the right branch and the epicardium presents great resemblances to the right branch, some of its muscle-fibers have even a clear central space so that this segment of musculature is indistinguish-

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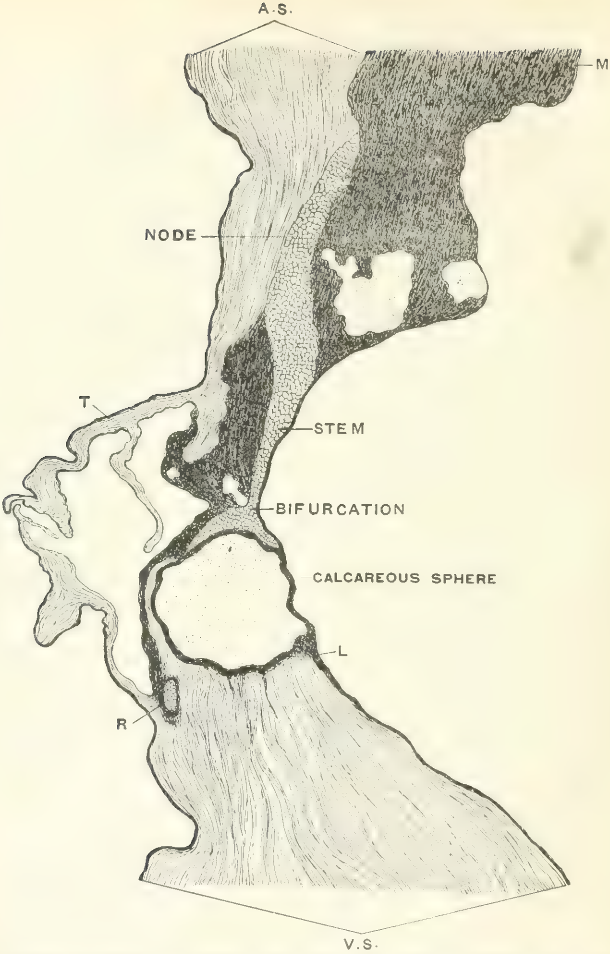
[3] In spite of the absolute break in the continuity of the right branch, impulses may yet have passed from the stump of the right limb through the ordinary ventricular musculature to the ventricular chamber, for it is not unlikely, judging by the anatomical findings in the hearts which we have studied and by physiological considerations, that the auriculoventricular system is not completely isolated between its two ends, namely, all along the line from the auriculonodal connection to the Purkinje fiber-ventricular junction.



Projection drawing of Sections 1438 and 1442, Case 1.—Showing an old calcareous focus, surrounded by connective tissue, which causes complete interruption of the bundle of His. At the bifurcation of the stem a calcific nodule (larger in the following sections) seems to press in upon it. This indented region of the body of the stem and the stumps of its two limbs present manifestly more thin-walled blood vessels and more connective tissue than is normal. At a lower level the necrosis encroaches on the stem to such an extent that it is entirely lacking in muscle-fibers for about 1 mm. from above down. Fibrous tissue is dark; necrotic material is dotted; *A-V* system is honeycombed; *A-S*, auricular septum; *L*, region where isolated left branch of *A-V* system appears in sections lower down; *M*, mitral valve; *R*, isolated right branch; *T*, tricuspid valve; *V-S*, ventricular septum.

able from the right branch as to its structure. Now and again the right limb presents more connective tissue than is found in the neighboring myocardium.

The left branch is characterized by somewhat more connective tissue and is on the whole somewhat paler staining than the surrounding musculature, with its individual muscle-fibers slightly coarser and not so densely constructed, though only rarely presenting a clear central space.

The vessels of both the specialized and typical musculature present sclerosis of the intimal and mesial coats. The muscles about the vessels (especially perhaps those of the outer coat of longitudinal fibers)[4] are finer and paler than the cross-striated typical cardiac muscle-fibers and resemble those of the nodal musculature of the heart. The capillaries are everywhere engorged and in places small extravasations have occurred into the tissues, possibly signifying nothing more than ante-mortem or post-mortem stasis.

There is a good deal of connective tissue in the interventricular septum but no evidence of recent inflammation. Besides the calcified area in the upper part of the interventricular septum (in the angle of bifurcation of the auriculoventricular system and crowding in on the stem) there are isolated areas with lime deposit in a region of much connective tissue between the right and left sides of the interventricular septum and in some connective tissue of the right ventricular musculature.

The smooth muscle of the left endocardium shows more connective tissue than normally. As usual, its muscle-fibers, like those about the vessels, resemble the muscle-fibers of the nodes of the heart.

The endocardium is normal, except that part of the left endocardium which covers the degenerated area where the cellular infiltration extends into it and dense connective tissue replaces the usual loose subendothelial tissue to quite an extent.

The epicardium of the posterior surface (the only epicardium on the sections) presents a thick, compact connective-tissue layer under a not inconsiderable part of the epithelium. In this layer there is (below the level of the node and stem) both a scattered and a dense cellular infiltration; that is, round cells, a few cells with larger cell body and larger vesicular nucleus, and an occasional polynuclear are found scattered and in masses. A most imposing focus of dense cellular infiltration is seen in the subepicardial fatty tissue immediately under the compact connective tissue layer in the lowest sections.

SUMMARY

Though the auriculonodal junction is not very powerful, it is not, apparently, inadequate, but there is an actual interruption of the continuity of the auriculoventricular structure along its course to account for the symptoms in this case; both branches of the conducting apparatus are cut off from the main stem of the auriculoventricular system and from each other. There is undoubtedly more connective tissue in the stem and more vascularity (with its attendant cellular infiltration) than is normal; and the upper ends of both limbs almost wholly and the body of the stem for about 1 mm. of its length have been demolished by a chronic, necrosing, calcifying process. In addition, there is an inconspicuous cellular infiltration at the node, as well as a more marked one of the stem and an imposing accumulation of round cells in the subepicardium; there is sclerosis throughout the coronaries and their intermuscular branches, and an increased amount of connective tissue in the ordinary ventricular musculature and some little calcific necrotic tissue.

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[4] This may be due to the direction in which they are cut. It should be noted that in this (as well as in other hearts) some of the ordinary cardiac musculature seems paler or more vacuolated than the rest owing to the direction in which the muscle-fibers are cut.

HEART 2

HEART 2.—*Case Report.*—The heart was forwarded to Dr. L. F. Barker of Johns Hopkins Hospital by Dr. D. A. Campbell, professor of medicine, Halifax, Nova Scotia, together with the following notes: "I first saw J. C., a retired mariner, in the summer of 1905, shortly after he was admitted to an institution for the care of the aged. He was then in his ninety-fifth year. His bodily health was excellent. He was quite corpulent, but unusually active. He was generally cheery and bright in disposition. His mental faculties were well preserved. Physical examinations disclosed the existence of some enlargement of the heart, and the presence of a very loud, harsh, aortic systolic murmur. The pulse rate was 60 and quite regular. During the following winter he had a sharp attack of influenza, from which he recovered completely. During the summer of 1906 he was ill the greater part of the time, but never wholly confined to bed. The most pronounced symptoms were: mental depression, cyanosis, bradycardia (the pulse-rate varying from 10 to 40 without any irregularity), slight seizures resembling petit mal occurring very frequently some days, and Cheyne-Stokes breathing especially at night. On account of the patient's being so fat, no superficial veins could be noticed in the neck. Various remedies were tried to afford relief without much success. Finally belladonna was given in moderate doses and improvement followed. That belladonna favorably influenced the conditions was evident from the fact that when the remedy was discontinued for ten days or so most of the symptoms returned.

"He continued to keep fairly well for a period of ten months, using the belladonna the greater part of the time.

"Early in August, 1907, the symptoms returned and gradually increased in severity, causing his death a month later. The bradycardia was not so marked as before, 30 being the lowest pulse-rate noted, and the epileptiform seizures were infrequent. The more prominent terminal symptoms were: marked cyanosis, Cheyne-Stokes breathing and total disappearance of the radial pulse and cardiac impulse for periods varying from thirty to sixty seconds in duration. This very unusual modification of the pulse was noted for five days before death, and seemed to be closely connected with Cheyne-Stokes respiration. The pulse usually, but not always, disappeared during the period of dyspnea, returning during the period of apnea. No sound whatever could be heard over the cardiac area when the radial pulsations were absent."

Macroscopic Examination of the Heart.—The heart was received from Dr. MacCallum in formaldehyd solution. Grossly the fixed heart presented no abnormality in the region of the conducting system which would account for heart-block.

Microscopic Examination of the Heart.—For microscopic examination the following blocks of tissue were excised:

1. The region of the sinu-auricular node. This block consisted of the auricular wall on either side of the sulcus terminalis of His extending posteriad as far as the interauricular septum and including a part of the superior and inferior venae cavae, and extending anteriad so as to include some of the pectinate musculature (a strip of about 0.5 cm.). Moreover, this block extended along both sides of the crest of the right auricle, thus including not only the part already described on the lateral aspect of the auricle on either side of the sulcus, but also the auricular wall on the median aspect facing the aorta. On the lateral aspect the area reached almost to the auriculoventricular groove; on the median face it

extended from the crest down for about 1 cm. toward the insertion of the aorta and was a continuation, as regards its width, of the lateral portion.

2. The auriculoventricular septum, containing the auriculoventricular node, the main stem, and the beginning of the branches. The sections were cut horizontally, approximately parallel to the stem.

3. A portion of the upper ventricular septum (left side) containing a part of the left branch of the bundle of His.

The first two pieces were embedded in celloidin-paraffin and cut in sections 15 microns thick. Every fifth section was mounted and stained with Weigert's iron-hematoxylin and van Gieson's picric acid fuchsin solution. A few sections were stained with orcein. The third piece was frozen, cut, and one section stained with Scharlach R, one section stained with iron-hematoxylin and van Gieson's solution, and finally one with orcein.

Sinu-Auricular Node Region.—The sinu-auricular node is sclerotic. There are small compact masses of connective tissue between the muscle-fibers; there is more connective tissue at the cephalic than at the caudal end of the node, where the muscle-fibers are separated by looser connective tissue instead of by "wads." Even allowing for individual variation within normal limits, the increase of connective tissue in this case is so marked throughout the entire extent of the node that it may be safely stated to be abnormal. No such fibrosis is present in the musculature immediately about the node or in the other portions of the right auricle examined. In the main the nodal fibers themselves may be described as lacking in cross striations. There is, however, the typical gradual transition from nodal into ordinary auricular musculature. The nodal artery, present in this heart, shows sclerosis of the media and a slight endarteritis. Some of the smaller branches too show these changes as do also the artery on its way to the node and some of the vessels among the ordinary cardiac musculature; occasionally a vessel presents obliterating arteritis. Some of the sections of the arteries have an outer layer of longitudinal smooth muscle-fibers arranged in small bundles.[5] Some of the nuclei of the auricular musculature are large and present uneven distribution of the chromatin and sometimes an irregular margin.[6]

Here and there in the pectinate and other ordinary cardiac musculature as well as in the specialized musculature of the Keith-Flack node, a very few cells which resemble lymphocytes are seen. They are slightly larger, have more cytoplasm, and their nuclei are more vesicular, less compact than those of lymphocytes. At one place in the nodal fat there is a small group of these cells. Larger collections of them appear in the epicardium and subepicardium; the largest at the level of the pace-making apparatus. Sometimes they are found about the subepicardial nervous elements in the neighborhood of the node. Now and again a nerve passes from the subepicardium into the sinu-auricular system. Once a ganglion cell was noticed alongside a capillary in the very center of the nodal tissue.

In general the effects of the pathological changes in the node of Keith and Flack are not yet established, and we do not venture on judging the significance of the sclerosis of this structure in this case.

Region of the Auriculoventricular System.—The connections between the auricular musculature and the node of Tawara are scanty. The node in the sections is an irregular semicircle, the diaméter of which lies along the central fibrous body, and the circumference of which is almost entirely surrounded by fat tissue, thus practically separating the nodal from the auricular musculature. There is an abnormal amount of fat tissue in the region of the interauricular septum. The node contains very little connective tissue.

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[5] Such bundles of longitudinal smooth muscle-fibers are normally found in all hearts.

[6] The nuclei of the swollen type mentioned above were described by Dr. A. E. Cohn in Heart, 1912, iv, 24.

Cross-sections of the artery in the specialized musculature present sclerosis of the intima and the media. Some of the very small vessels have a marked diminution of their lumina; but it is impossible to say which of the two inner coats is involved. There is intimal and mesial sclerosis of the arteries in the interauricular and interventricular septa, and of the coronary artery (with atheroma). There is calcific deposit in the wall of the aorta not only near the opening of the right coronary but even nearer to the auriculoventricular system than that.[7]

As was to be expected in sections of a heart from a patient advanced in years, lipochrome granules are seen in the muscles of the auricle, ventricle, and auriculoventricular system. Some of the nuclei of both the auricular and the ventricular muscles were of the "swollen" type already described. The smooth muscle of the left endocardium presents increase of connective tissue as does the ordinary interventricular musculature especially on the left side.

Though the stem is long and slender, there is nowhere a break in the continuity of the auriculoventricular system.

Upper Ventricular Septum.—The piece from the upper part of the septum on the left side of the heart presents an increased amount of connective tissue in the ordinary cardiac musculature but no evidence of recent inflammation. There is also a slight increase in the connective tissue surrounding some of the vessels; all three vessel coats are sclerotic. There is no fatty infiltration of any of the musculature. The endocardium appears to be normal.

SUMMARY

While it cannot be affirmed that the slightness of the auriculonodal junction is the causative factor in this case of Adams-Stokes disease, yet it is of importance in the light of the fact that Armstrong and Mönckeberg[8] reported an exquisite case of lymphangio-endothelioma of the auriculoventricular node in which it was judged that the break between auricular and nodal musculature was the cause of the heart-block.

The condition of the blood-vessels in the aged patient may have been an accessory factor.

We should expect to find some cellular infiltration in arteriosclerotic hearts, and we do not know that there is any relation between the increase of cells in the interstitial tissue of the sinu-auricular node and of some of the ordinary auricular musculature and the clinical symptoms in this case.

It should be recalled that the interventricular septum, especially on the left side of the heart, presents an increased amount of connective tissue, and that some of the nuclei were of the "swollen" type with scattered chromatin and sometimes with irregular margin.

In brief, the most obvious explanation of the symptoms in this case is the auriculonodal break.

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[7] In another heart (from a patient without data as to heart-block) though calcareous nodules were found grossly in the neighborhood of the bundle of His, microscopically these did not interfere with the continuity of the auriculoventricular system. This heart was kindly given us for examination by Dr. W. G. MacCallum.

[8] Armstrong and Mönckeberg: Arch. f. klin. Med., 1911, cii, 144.

HEART 3

HEART 3.—*Clinical History.*—The heart was received from Dr. W. G. MacCallum, who performed the autopsy and gave us the clinical notes furnished him by Dr. M. G. Porter.

The patient was a white man aged 50. There was no history of syphilis; he had not used alcohol to excess. He had always been strong and healthy until eighteen months before exitus, when he had suffered from several attacks of syncope within a few days. Six months before his death he had a similar seizure and since that time he had frequently complained of giddiness on rising and of shortness of breath. Three days before his death he was seized, after violent exertion, with severe pain in his precordium, radiating down both arms. Subsequently he had repeated attacks of syncope and several epileptiform convulsions with attacks of bradycardia between which the pulse rhythm would be normal. The pulse-rate ranged between 110 and 25 beats per minute. He died in one of his seizures. The urine was acid, specific gravity 1.018, trace of albumin, no sugar. On the day previous to his death a distinct pericardial friction rub was heard over the body of the heart. This was again heard about an hour later ("pericarditis epistenocardia").[9]

Autopsy.—The autopsy revealed the cause of death to be rupture of the wall of the heart and consequent hemopericardium. "The pericardium was found to be filled with blood which was partly clotted: in places the clot was fully 1 cm. thick. There was a ragged hole in the anterior wall of the left ventricle about 1 cm. to the left of the vein that corresponds to the interventricular septum. Some blood-clot was adherent to and extended into this ragged opening. The interventricular septum throughout its entire extent was opaque, of a grayish ochre color and was evidently necrotic. This appearance extended to within 1 cm. of the pulmonary orifice where it was sharply marked off from the adjacent normal heart wall. The wall of the left ventricle was greatly hypertrophied, but its tissue was not abnormal.

"The trabeculae were opaque and frequently broken through. In the angle between the wall of the ventricle and the septum was a hole, through which a probe was passed until it extended through the opening on the anterior surface of the heart. Both coronaries were markedly sclerotic. The anterior descending branch of the left coronary artery was completely occluded by a thrombus 3.5 cm. from its orifice. The sequence of events has evidently been: coronary sclerosis, thrombosis of the left descending branch, infarction of the interventricular septum, rupture of the heart wall, hemopericardium."[10]

Grossly, then, the heart presented an infarction of the interventricular septum including the neighborhood of the main stem of the bundle of His and its branches.

Microscopic Examination of the Heart.—The heart was received from Dr. MacCallum in formaldehyd solution. For microscopic examination the following blocks of tissue were excised:

1. The region of the sinu-auricular node as described under Heart 2.

2. The auriculoventricular septum containing the auriculoventricular node, the main stem and the beginning of the branches.

3. The ventricular septum adjacent to Block 2 (just below it) with the posterior papillary muscle of the left side and the underlying ventricular wall and a piece of the apex.

4. A portion of the upper ventricular septum (left side) containing a part of the left branch of the bundle of His.

5. The anterior papillary muscle of the right ventricle with chordae tendineae.

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[9] Sternberg: Compt. rend. XVI Cong. internat. méd., Budapest, 1909, Section VI, Méd. Interne, p. 396; Verhandl. d. XXIX Deutsch. Cong. f. inn. Med., 1912, p. 444.

[10] MacCallum: Johns Hopkins Hosp. Bull., February, 1908, No. 203, xix, 50.

6. The base of the anterior papillary muscle of the left ventricle and the underlying ventricular wall.

7. A portion of the wall of the left auricle.

Blocks 1, 2 and 4 were embedded, cut, mounted and stained like the corresponding pieces in Heart 2; piece 3 like blocks 1 and 2 above except that only every fortieth section was stained. The remaining blocks of tissue (5, 6 and 7) were embedded in celloidin-paraffin, cut 15 microns thick and two sections of each stained.

Left Auricle (Block 7).—To begin with the least important block of tissue: The epicardium and adjoining fat and muscle of the wall of the left auricle present cellular infiltration (only an occasional polymorphonuclear leukocyte here). The infiltration is most marked in the epicardium and subepicardium; one small focus was seen in the endocardium. There is sclerosis of the media and intima of the vessels.

Region of the Sinu-Auricular Node (Block 1).—Unlike the portions from the interventricular septum, the block of tissue in the region of the sinu-auricular node presents a comparatively slight cellular infiltration. The round cells (only a few polynuclears are to be seen) are present in the epicardium and subepicardium, to a less extent in the nodal tissue, and to still less an extent in the ordinary myocardium. There is practically no invasion of the endocardium. The area near the inferior vena cava is somewhat more involved than the rest of the ordinary cardiac musculature. The most marked infiltration in this block is found in two regions, namely: (1) in the epicardium at the level of the node and (2) about the subepicardial nervous elements and the musculature on the median face of the crest near the interauricular septum (i. e., the region of the synapse of the vagus as described by Marchand and Meyer[11]). There is a negligible increase in the amount of connective tissue in the head of the pacemaking apparatus. The nodal muscle-fibers are much coarser than those of Heart 2 and show cross-striations clearly. There is the usual gradual transition into ordinary cardiac musculature. There are a few pus cells in the media of the nodal artery. The vessels, both of the specialized and typical musculature, present sclerosis of the two inner coats. As usual, some of the sections of the arteries present an outer layer consisting of bundles of longitudinal non-striated muscles. Some of the nuclei of the musculature of this piece of tissue are of the swollen type. At one point the node encloses ordinary musculature. Here and there a nerve-fiber from the subepicardium is seen to enter the nodal structure; and in its very center a ganglion cell was observed.

It does not seem possible that the very slight cellular infiltration of the pacemaking system in this case could account for any decided influence on the functions of the heart.

Region of the Upper Auriculoventricular System (Block 2).—A very few infiltrating cells — for the most part lymphocytic, rarely polymorphonuclear — are seen in the conducting system. The right branch, and the stem (at the level of its division into two branches) and the central fibrous body near by present more pus cells than the node, the upper stem, and the left branch. Close at hand, at the basal end of the ventricular septum is an infected infarct with pus cells in the capillaries and adjoining tissues. There are pus cells elsewhere (everywhere round cells exceed the polynuclears in numbers), namely in the epicardium, subepicardial fat, auricular musculature, endocardium, tricuspid and mitral and aortic valves. But the most pronounced lesion in this block is situated in the typical ventricular musculature *near* the junctional tissue. Here the musculature has taken an unusual brown tint and many of the muscle nuclei seem to have disappeared. Indeed, some of the muscle-fibers themselves have apparently disappeared in their entirety and have been replaced by connective tissue. The remaining muscle-fibers are separated by columns and masses of pus cells and are shrunken. The central fibrous body is a little larger than normal. Practically all the vessels present intimal and medial sclerosis; such are the nodal artery, the aorta, the coronary artery, and, in brief, other vessels in the auricular and ventricular septa. Some of the nuclei of this block of tissue are of the swollen type. The smooth muscle of the left endocardium is normal.

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[11] Marchand and Meyer: Arch. f. d. ges. Physiol., (Pflueger's), 1912, cxlv, 401.

Region of the Lower Auriculoventricular System and of the Terminal Arborizations (Blocks 3, 4, 5, 6).—Upper Ventricular Septum: In Block 4, that is, the piece from the upper part of the septum on the left side of the heart, there is histological evidence of the infarction just as there is in the other blocks from the interventricular septum. There is a round-celled and polymorphonuclear infiltration of the endocardium, subendocardium, the region of the left branch and especially of the ordinary ventricular musculature where many of the muscle-fibers are separated from one another by pus cells, are shrunken, and, though still showing cross-striations, are lacking in nuclei. Some of the muscle-fibers have indeed apparently quite disappeared. There is fat in both the region of the specialized and ordinary cardiac muscles.

Region of the Terminal Arborizations.—In Block 3, namely, the ventricular septum immediately below Block 2, no attempt was made to find and trace the right branch of the auriculoventricular system. The uppermost part of the posterior limb of the left branch was identified macroscopically as if for dissection and marked with India ink[12] and so found in the sections under the microscope; but as we did not follow the left branch continuously in serial sections from the stem on, we cannot assert that we have identified it. In this piece three, there is in the ordinary ventricular musculature, including that of the apex, a continuation of the same lesion (an infected infarct) as described for the other pieces from the ventricular septum, namely, pieces two and four. In that portion of the left limb which was marked with India ink there was no cellular infiltration; but ventral (anterior) of this region there is some infiltration of the endocardium and subendocardial musculature where it is not unlikely that the left branch is involved. Similarly there is infiltration of the endocardium and subendocardial musculature in the apex. On the other hand there is no cellular infiltration of the posterior papillary muscle of the left side. Many of the cells under the epicardium and endocardium of the right and left ventricle and of the posterior papillary muscle are broad and pale and vacuolated; some of these may be Purkinje cells, possibly some Purkinje-like because of the direction in which they are cut and others perhaps because of a Purkinje-cell variety of muscle atrophy.[13] Some of the nuclei of the cells are of the swollen type with unevenly distributed chromatin and irregular margins. The coats of the blood-vessels present an increased amount of connective tissue.

The anterior papillary muscle and chordae tendineae of the right side (Block 5) are normal except for some nuclei of the swollen type; the base of the anterior papillary muscle of the left side and underlying ventricular wall (Block 6) present pus cells in the epicardium and subepicardium and sclerosis of the two inner coats of the vessels.

In short, an almost negligible number of lymphocytic and a still lesser number of polymorphonuclear cells have invaded the auriculoventricular system, and that is all; therefore from an anatomical standpoint the conducting mechanism is in a condition to functionate, but from a physiological viewpoint the sclerosis of its vessels and the presence of even but a few pus cells in the junctional tissue and finally the neighboring infected infarct suggest an inefficiency of circulation and an abnormal condition sufficient to account for heart-block.

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[12] According to Nagayo [in Beiter. z. path. Anat. u. z. allg. Path. (Ziegler's) 1909, xlv, 295] the stripes seen macroscopically are due not only to the presence of the branches of the conducting system, but also to bundles of smooth muscle fibers.

[13] Cohn and Lewis: Heart, 1912, iv, 24.

DISCUSSION

The sclerosis of the coronary arteries and its branches in these three aged patients suggests that an inadequate circulation played a part in the production of the symptoms of Adams-Stokes syndrome in all three.

As was expected in arteriosclerotic hearts, some increase of the cells in the interstitial tissue was observed, but we do not know what may have been its significance in these cases.

If these are three cases of heart-block, as is suggested by the Adams-Stokes syndrome, then they form a series, Case 1 with an absolute break between the stem at its bifurcation and the two limbs right and left, Case 2 with its inadequate auriculonodal junction and Case 3 without a break in the continuity of the auriculoventricular system.

In the first case described, a lesion to account for heart-block was seen; there was complete transverse destruction of the tissue of the bundle of His. In the second case, it is impossible to state to what extent the sclerosis of the sinu-auricular node and the fact that the auriculonodal junction is slight, affected the functions of the heart. And in the other case, though histological investigation brought to light no such lesion of the auriculoventricular system (i. e., partial or complete break in its continuity), as has been frequently regarded the ultimate anatomical basis of the affection, yet the findings are indicative of such a disturbed circulation and abnormal condition in the neighborhood of the conducting apparatus as might profoundly influence its functional capacity.

SUMMARY

1. The hearts of three patients with Adams-Stokes syndrome presented, the first a calcific mass in the region of the auriculoventricular bundle, the second no gross lesion across the conducting system to account for the symptoms, the third infarction of the ventricular septum.

2. The first patient is reported to have denied a syphilitic history, in the second case the past history is not given, and the third patient is said to have had no lues. All three were well along in years with some sclerosis of the vessels and some increase of cells in the interstitial tissues.

3. The most noteworthy lesions in each case were: in the first, an absolute break in the course of the stem of the auriculoventricular system; in the second, the slight auriculonodal junction and a sclerosis of the sinu-auricular node; in the third, an infected infarct of the ordinary ventricular musculature near the junctional tissue.

4. The possibility of insufficient circulation and of a lesion in the ordinary ventricular musculature as agents in the production of heart-block, are suggested.

We are greatly indebted to Dr. W. G. MacCallum and Dr. L. F. Bishop for the privilege of describing these cases and to Dr. A. E. Cohn for his valuable suggestions.

THE INTRAMENINGEAL TREATMENT OF TABES AND CEREBROSPINAL SYPHILIS *

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The treatment of syphilis of the central nervous system has always been unsatisfactory. The cerebrospinal system is a closed one, and the diffusion of drugs from the circulating blood into the cerebrospinal fluid is slow and incomplete. For this reason organisms which have invaded the nervous tissue or meninges remain more or less protected from the drugs which may be present in the vascular system. For a number of years the desirability of the direct application of antisyphilitic drugs has been recognized. Horsley[1] went so far as to advocate the "heroic" treatment of opening into the subdural space and washing out with mercuric chlorid (1:1,000) solution, but this procedure proved too irritating.

With the advent of salvarsan and neosalvarsan, hope was entertained that this therapeutic agent could be injected intraspinally; but investigation showed that it also damaged the tissues. Wechselmann[2] found that small amounts (1 mg.) when injected into the brains of dogs and rabbits at a concentration of 1:500 and 1:1,000 produced convulsions, weakness of the limbs and death in from two to fourteen days; but small doses, from 0.5 to 0.25 mg., in greater dilution (from 1:2,000 to 1:4,000) caused no reaction. Later he reported[3] the intraspinous injection of neosalvarsan in four patients without reaction, giving each from 0.5 mg. to 3 mg. Marinesco[4] reports thirteen cases in which neosalvarsan was given intraspinally, the dose averaging about 5 mg. In two patients no reaction occurred, but in the remainder the reaction was severe; thus, eight patients developed incontinence of urine or retention, three showed weakness of the extremities and in one case anesthesia of the rectum, legs and buttocks occurred. Ellis and Swift[5] have carefully studied the effects of the intraspinous injection of salvarsan and neosalvarsan in monkeys. They injected small quantities and considered the cell-count as an indication of reaction due to irritation.

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* From the Medical Clinic of the City Hospital at Bay View.

[1] Horsley, V.: Neurol. Centralbl., 1910, xxiv, 257.

[2] Wechselmann, W.: Die Behandlung des Syphilis mit Dioxydiamidoarsenobenzol, "Ehrlich-Hata 606," Berlin, 1911, p. 11.

[3] Wechselmann, W.: Deutsch. med. Wchnschr., 1912, xxxviii, 1446.

[4] Marinesco: Diatet. u. physik. Therap., 1913, xvii, 194.

[5] Swift and Ellis: Jour. Exper. Med., 1913, xviii, 428.

They found that the intraspinal injection of even minute quantities (0.2 mg.) produced profound cellular reactions which persisted over ten days, while 3.2 mg. caused, in one monkey, paralysis of the hind legs, which lasted several months. The injections of neosalvarsan were, on the whole, less severe, but still gave evidence of irritation in doses as small as 0.045 mg. Repeating the injection seemed to increase these effects.

The study of the effects of the intravenous or intramuscular injection of salvarsan brought to light a very important fact. Plaut[6] showed that the serum of patients who have received salvarsan exerts a definite antisyphilitic effect, whereas normal serum has no such activity, and the serum of patients treated with iodids and mercury has very little such power. Meirowsky and Hartman[7] and Gibbs and Calthrop[8] treated cases of syphilis with good results by injecting subcutaneously serum taken from other patients who had received salvarsan. In the same way Henry Alsten[9] successfully treated several cases of frambesia. Ellis and Swift[10] took up the study of this serum and showed that, when taken from the patient within six hours after the salvarsan injection, it inhibits the growth of the *Treponema pallidum*, but if taken before treatment, or from six to twenty-four hours after treatment, there is no inhibition. They also reported beneficial effects from the intraspinal injection of this serum, with very few irritative phenomena.

This spirochetacidal activity of salvarsanized serum was further studied by Gonder,[11] Castelli,[12] and Ellis and Swift,[13] who showed by the use of animals that it had a marked effect on the virulence of several spirochetes, and that this effect was demonstrable only by the injection into animals of the organisms so treated. Thus, Swift and Ellis[13] showed that the serum of rabbits treated intravenously with salvarsan, and the serum of patients treated likewise with salvarsan or neosalvarsan exerted an inhibitory effect on the *Spirochaeta duttoni;* and that these spirochetes did not appear objectively (dark field) changed, but they would not cause infection in animals into which they were injected. These investigators also found that heating the serum at 56 C. (132.8 F.) for half an hour markedly increased the activity of the serum, and that this increase is due only in part to the destruction of some inhibiting substance. They also showed that the cerebrospinal fluid does not possess these inhibitory bodies.

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[6] Plaut: Deutsch. med. Wchnschr., 1910, xxxvi, 2237.

[7] Meirowsky and Hartman: Med. Klin., 1910, vi, 1572.

[8] Gibbs and Calthrop: British Med. Jour., 1911, i, 809.

[9] Alsten, Henry: British Med. Jour., 1911, i, 360.

[10] Swift and Ellis: New York Med. Jour., 1912, xcvi, 53-55.

[11] Gonder, R.: Ztschr. f. Immunitätsforsch., Orig., 1912, xv, 57.

[12] Castelli, G.: Ztschr. f. Chemotherap., Orig., 1912, i, 122 and 167.

[13] Swift and Ellis: Jour. Exper. Med., 1913, xviii, 435.

The intraspinal injection of serum, taken an hour after the intravenous administration of salvarsan, was first employed by Swift and Ellis as a method of treating cerebrospinal syphilis. Their technic[14] was, in brief, the following: One hour after the intravenous injection of salvarsan 40 c.c. of blood are withdrawn directly into a bottle-shaped centrifuge tube, and allowed to coagulate, after which it is centrifugalized. The following day 12 c.c. of this serum are pipetted off and diluted with 18 c.c. of normal saline solution. This 40 per cent. solution is then heated at 56 C. for half an hour. By lumbar puncture the cerebrospinal fluid is withdrawn until the pressure is reduced to 30 mm. (water), after which enough of the serum solution is run in by gravity exactly to replace the cerebrospinal fluid withdrawn.

During the past year and a half the cases of cerebrospinal syphilis in the City Hospital at Bay View have been treated along the lines laid down by Ellis and Swift, with one important change—we injected undiluted serum in large quantities (25-35 c.c.). Thus, there was given, in many instances, twice as much actual serum at a single injection as was given by Ellis and Swift. The technic was the following: Salvarsan, 0.6 gm., was given intravenously, having been made up in water distilled within an hour of time of using, and the solution was injected at once. One hour later from 75 to 100 c.c. of blood were withdrawn into a large, sterile tube, and this was set aside to clot. After from one to eighteen hours the serum was pipetted off and centrifugalized at high speed for fifteen minutes in order to throw down any red blood-corpuscles present. The serum was then heated in a water-bath at 56 C. for half an hour and the intraspinal injection made at once. A lumbar puncture was done and the spinal fluid was slowly and carefully drained off into a graduated sterile cylinder. Not more than 35 c.c. were removed. The serum was then injected, a syringe and two-way stop-cock being used, the serum being drawn back into the syringe from the flask and then slowly injected through the needle. Great care was taken not to use any undue pressure in running in the serum. Enough was injected to replace exactly the amount of spinal fluid removed, whether this was only a few cubic centimeters or as much as 35 c.c. After the injection all pillows were removed, the foot of the bed elevated and the patient kept on his back in this position for at least an hour. The treatments were repeated at intervals of seven to twenty days, when possible, depending in part on the way in which the patient reacted.

The brief protocols of eight unselected cases are appended as illustrative of the method, with note of some of the difficulties and dangers, and the results achieved. Some cases are still under treatment at the time of this report.

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[14] Swift and Ellis: The Archives Int. Med., 1913, xii, 331.

REPORT OF CASES

Case 1.—An unmarried colored laundress, aged 37, was admitted suffering from tertiary syphilis with cerebrospinal infection and syphilitic cerebral thrombosis.

History.—The primary infection occurred twenty years before onset of present illness. No secondaries showed but tertiary lesions appeared during the past five years. The patient had had slight, irregular mercurial treatment during past five years. Severe frontal headaches had existed for a week before admission, with the development of flaccid, left-side paralysis, which came on suddenly eighteen hours before admission with no loss of consciousness or convulsions.

Examination.—Complete left-side paralysis, which included the muscles of the face, arm and leg, with moderately exaggerated deep reflexes and positive Babinski's sign. Neck stiff and retracted. Several large, luetic ulcerations over lower abdomen.

Treatment and Result.—After admission the patient was given three injections of salvarsan and two intraspinal injections. In the first treatment blood was withdrawn seventy-two hours after the injection, and in the second twenty-four hours after injection. When discharged the patient was normal physically except for a slight residual paralysis of the flexors of the left forearm and a left pes equinus. On admission the cerebrospinal fluid showed twenty cells per cubic millimeter; when discharged there were seven cells per cubic millimeter. Wassermann was positive on admission, negative when patient was discharged.

Case 2.—A married, white window-washer aged 44, was admitted ill with tabes dorsalis.

History.—Primary infection had occurred twenty years before admission. The present illness began five years before admission with sharp, shooting pains in the legs. Extreme ataxia had developed in past two years. The patient had had six weeks' treatment in a German army hospital at the time of primary chancre. About two months later he was given another short course of iodids and mercury.

Examination.—No sphincter disturbances. Argyll Robertson pupils present, knee-jerks absent, muscle sense in legs much impaired, marked ataxia, causing great difficulty in walking.

Treatment and Result.—Two intravenous injections of salvarsan and two intraspinal injections were given with consequent improvement. On admission the patient was very ataxic and suffering severely with lightning pains. After the second treatment the lightning pains had ceased entirely and he could walk much better. He felt so much improved that he refused to remain for further treatments.

Case 3.—An unmarried white man, a clerk, aged 37, on admission was found to be afflicted with tabes dorsalis.

History.—The primary infection had occurred nine years prior to admission and seven years before onset of present illness, which was accompanied with lightning pains, gradually increasing unsteadiness in walking and dimness of vision. Bladder symptoms developed about a year after onset. At the time of the primary chancre the patient had local treatment and took pills by mouth for one month; during the past eighteen months, mercury and iodids continuously. One year ago he was given an intramuscular injection of salvarsan and a second three months later.

Examination.—Argyll Robertson pupils. General enlargement of lymph-nodes. Knee-jerks absent, muscle sense completely absent in the legs, moderate dulling of tactile and pain sense. Romberg sign markedly positive. Positive Wassermann in blood-serum and spinal fluid and ten cells per cubic millimeter in spinal fluid.

Treatment and Result.—Four intravenous injections of salvarsan, three of neosalvarsan, and six intraspinal injections were given. Total: salvarsan 2.7 gm., serum 116 c.c.; time, seventy-nine days. On admission the patient was unable to walk on account of the ataxia. At present he walks fairly well without assistance. He is now free from the lightning pains. The cells in the spinal fluid dropped from ten to six per cubic millimeter, and Wassermann reaction has changed from complete fixation to a very faint fixation. The reactions were very severe, prostrating the patient, and for this reason the treatments were discontinued.

Case 4.—An unmarried, white salesman, aged 37, was admitted with cerebrospinal syphilis and syphilitic lateral sclerosis.

History.—The primary infection was incurred fifteen years before onset of present illness two and a half years ago, when unsteadiness in walking developed, soon followed by weakness and stiffness of the legs. Paresthesias, numbness, girdle sensations and bladder symptoms developed within eighteen months. The patient has had several short mercurial courses by mouth and by inunction.

Examination.—General enlargement of lymph-nodes. Pupils unequal but react normally. Knee-jerks greatly exaggerated on both sides; ankle-clonus present and Babinski sign positive. Legs stiff and spastic and held in adduction. Patient walks with difficulty. Wassermann on blood-serum, 60 per cent fixation. Positive Wassermann and twenty-five cells per cubic millimeter in cerebrospinal fluid.

Treatment and Result.—Two intravenous injections of neosalvarsan, six of salvarsan and eight intraspinal injections were given; total: salvarsan, 3.9 gm., serum 178 c.c.; time, 195 days (two admissions). On admission the patient was so spastic as to be unable to stand on his feet and he was suffering severely with girdle sensations. These disappeared immediately and the spasticity became distinctly less marked until he can now walk without assistance and can go up and down stairs. In the spinal fluid the cells have fallen from twenty-five to five per cubic millimeter, and the Wassermann from complete fixation to very faint fixation.

Case 5.—A married white man, blacksmith, aged 45, was admitted with tabes dorsalis, partial optic atrophy and tertiary syphilis.

History.—Primary infection appeared as a chancre twenty-two years before admission. Present illness began four years before admission with dimness of vision, soon followed by lightning pains which have gradually become more and more intense. Unsteadiness in gait has developed during the past two years; no sphincter disturbances. At the time the chancre appeared a few local applications of calomel powder were made; no medicine was given internally. During the past four years the patient has had more or less continuous treatment with mercury and iodids.

Examination.—Moderate enlargement of lymph-nodes. Argyll Robertson pupils and primary optic atrophy. Knee-jerks absent; moderate ataxia of legs. Positive Wassermann and thirty-five cells per cubic millimeter in spinal fluid. Wassermann in blood-serum negative.

Treatment and Result.—Eight intravenous injections of salvarsan and eight intraspinal injections were given; total: salvarsan, 4 gm.; serum, 204 c.c.; time, 108 days. This patient had been unable to work for six months on account of the severe lightning pains. After the first treatment he was entirely free from pains except for one mild attack. The cell-count in the spinal fluid fell from thirty-five to five per cubic millimeter, and the Wassermann from positive to negative.

Case 6.—A white man, bookkeeper, widower, aged 54, was admitted suffering from tabes dorsalis.

History.—Primary infection occurred twenty-four years prior to admission. Initial lesion was not known, possibly a chancre. Two years before admission the patient had an acute retention of urine, and examination at that time showed inactive pupils, knee-jerks faint, bladder atonic and anesthetic, and a positive Wassermann in spinal fluid. Eighteen months ago he began to suffer with severe pains in the back, coming on in paroxysms about every half hour, worse at night. A hemiplegia, three years ago has cleared up almost completely, the right side having been involved. The patient has had several short courses of iodids and mercury by mouth during the past two years.

Examination.—Argyll Robertson pupils. Unilateral sweating involving the whole left side of the head and neck. Slight residual weakness and exaggeration of reflexes of right arm and leg. Knee-jerk almost absent on left. Wassermann in blood-serum negative. Positive Wassermann and sixty-two cells per cubic millimeter in spinal fluid.

Treatment and Result.—Two intravenous injections of neosalvarsan, seven of salvarsan and nine intraspinal injections were given. Total: 3.9 gm., serum, 186 c.c.; time, seventy-seven days. When admitted the patient was almost prostrated on account of the severe and constant pain in the back. This steadily became less intense and the patient was quite comfortable when discharged. The cells in the spinal fluid fell from sixty-two to four per cubic millimeter and the Wassermann changed from positive to negative.

CASE 7.—An unmarried colored man, a cook, aged 45, was admitted under diagnosis of tabes dorsalis with optic atrophy.

History.—The primary infection had occurred twenty-seven years before onset of present illness, which began five years before admission, with unsteadiness and weakness of the legs; the subsequent history is typical. There has been incontinence of urine for three years. Lightning pains have been constant but not severe. Numerous gastric and laryngeal crises have occurred during the past year. The patient has had failing vision for eighteen months. For the past year the ataxia has been so severe that he has been practically helpless. The patient had a short course of local treatment at time of chancre; mercury and iodids by mouth during past year.

Examination.—Patient greatly emaciated. Complete loss of muscle sense in the arms and legs with exaggerated ataxia of the muscles of the face, arms and legs. Argyll Robertson pupils. Deep reflexes of arms and legs absent. Wassermann in blood-serum negative. Positive Wassermann and thirty-six cells per cubic millimeter in spinal fluid.

Treatment and Result.—Three intravenous injections of salvarsan and two intraspinal injections were given. Total: salvarsan, 1.2 gm.; serum, 35 c.c.; time, thirty-six days. Patient suffered an extreme reaction after the second intraspinal injection which was characterized by severe respiratory depression. Immediately after the injection, at 4 p. m., it was noticed that the patient seemed slightly dazed and did not answer questions so quickly as usual, although he was perfectly rational. Twenty minutes later the mouth began to twitch and pull to the right, the eyes turned to the right, and the right arm and leg began to jerk slightly. The respirations suddenly dropped to four a minute, and were very irregular, the sequence usually being two or three spasmodic respirations followed by a long period of apnea, sometimes lasting three-quarters of a minute. The jerking and twitching soon ceased and the patient became quite flaccid. At 6 p. m. it became necessary to give artificial respiration for about half an hour. A lumbar puncture was done at 7 p. m., and 10 c.c. of the spinal fluid, tinged with the serum, were allowed to drop out. At 8 p. m. another puncture was done and the spinal canal washed out three times with normal saline. It was noticed that the intraspinal pressure varied with the respirations in the normal manner, and there was no noticeable change in the condition of the patient when the canal was drained or filled with 35 c.c. of normal saline. The condition of the patient remained about the same until 1 a. m., when he suddenly sat up in bed, recognized those about him and talked rationally. In about fifteen minutes he again suddenly sank into apparent coma, with spasmodic and irregular respirations, four or five to the minute, and remained thus until 4 a. m., when, as before, he suddenly recovered, was perfectly rational and showed no signs of weakness. When questioned the patient asserted he was entirely conscious at all times and told with a fair degree of accuracy what was done and who was in the room. He suffered no pain, but simply could not breathe, although he felt a great desire to do so. The next day he was as well as usual. No more treatments were given and he left the hospital in a week, unimproved.

Case 8.—An unmarried white man, a painter, aged 47, was admitted suffering from cerebrospinal syphilis.

History.—The primary infection occurred twenty-six years before admission. The patient was admitted on account of acute alcoholism. When examined the eyes showed Argyll Robertson pupils. For the past year he has suffered with pains in the back and giddiness. The patient had a short course of local treatment at time of chancre.

Examination.—Reflexes all normal, knee-jerks active. Wassermann on blood-serum negative. Faintly positive Wassermann and fifty-four cells per cubic millimeter in spinal fluid.

Treatment and Result.—Four intravenous injections of salvarsan and four intraspinal injections were given. Total: salvarsan, 2.4 gm.; serum, 118 c.c.; time, thirty-six days. The cells in the spinal fluid dropped from fifty-three to ten per cubic millimeter; the Wassermann remained positive. The patient felt perfectly well and could not be induced to remain longer in the hospital.

From the foregoing cases it is evident that the intraspinal method is a step forward in the treatment of tabes and cerebrospinal syphilis. The patients were uniformly relieved from pain, and as far as locomotion is concerned there was a slow but definite improvement, in some instances amounting almost to restitution to normal. It is in this respect that our cases seemed to do better than those of Swift and Ellis, perhaps on account of the larger doses of serum.

The psychic effect of the treatment is also marked. The patients became encouraged by the quick relief of pain and the first improvements in the control of motion and were faithful in their efforts to use the legs and practice walking, stair climbing, etc. The nutrition also rapidly improved under these stimuli. In fact, this very improvement was a hindrance in our series, for with the class of people under our care it was in most instances impossible to keep them in the hospital long enough to carry the treatment as far as we should have liked to do.

The effect of the treatment on the cerebrospinal fluid was very striking. The cell-count first fell to normal, the Wassermann reaction becoming negative some time after the cells were reduced. It has seemed from our observations that the Noguchi reaction was of little value during the carrying out of this treatment, since such large amounts of globulin were injected into the spinal canal. At any rate, the Noguchi reactions were positive, in most instances, after the cell-count and Wassermann indicated a normal fluid.

Where the patients are intelligent enough to appreciate the necessity for repetition of the treatment until the biologic indices of normal are maintained, there need be but transient interruptions of regular occupation, lasting forty-eight to seventy-two hours as a rule. It is also true that while the risks are minimal, they do exist and in all probability very feeble, advanced tabetics or very acute cases of cerebrospinal lues should not be treated in this way.[15]

In those of our cases which were treated with the undiluted serum the reactions were sometimes more severe than those reported by Swift and Ellis—pain in the abdomen, legs and rectum, with occasional nausea and vomiting or dizziness, and in a few instances a little fever. We do not feel, however, that these constitute any contra-indication to the larger doses of whole serum, especially in the light of the apparently greater benefit to the patient. The reactions produced by the injection of the salvarsanized serum from another patient were very severe, as shown by two of our cases, the donors of the serum receiving an equal quantity of the same lot, at the same time and in the same way, having no reaction at all.

It is quite evident that so indirect a method of applying arsenic in the treatment of syphilis of the central nervous system cannot be considered as final; but we believe it is an advance on what has gone before and a spur to the findings of new preparations or new methods more suitable for the accomplishment of the desired results.

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[15] One of us has treated by this method a tabetic with diabetes mellitus. The patient was told of the risk, but wanted to take any chance. He had had five previous intravenous treatments with salvarsan. Eighteen hours after the injection of 20 c.c. of salvarsanized serum he developed diabetic coma and was very ill for five days, when a large intravenous transfusion of sodium carbonate and glucose turned the scale and he recovered from the coma. He was not benefited by the treatment except in the disappearance of the lightning pains.

TWENTY-THREE CASES OF PNEUMONIA TREATED WITH ANTIPNEUMOCOCCUS SERUM *

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Through the cooperation of the Research Laboratory I was able to give a series of patients suffering from lobar pneumonia an antipneumococcus serum, and although the results were somewhat inconclusive, it seems desirable to publish them.

The series includes practically all of the pneumonia patients admitted to the service of the Second Medical Division of New York Hospital during the period of the test. This division receives all medical patients admitted to the hospital on the even days of the month, while those admitted on the odd days go to the first division. Although this method of assignment does not give a strict alternation of patients, yet it seemed justifiable to use the patients on the first division as controls, inasmuch as none of them received any serum.

The serum was taken from a horse immunized against many strains of pneumococci.[1] Usually it was injected directly into a vein of the arm at a temperature about that of the patient. This rule was departed from and the serum was given subcutaneously to two children on account of the difficulty of entering the vein with the needle, and also when second and later doses were given to four adult patients who had received the initial dose intravenously. The first doses for adults in the earlier cases was 100 c.c. This was increased later until, in one instance, an initial dose of 300 c.c. was given. Many of the patients received more than one dose so that the total amount of serum that an individual received ranged from 50 to 750 c.c. This maximal quantity was given in six doses spread over a period of five days.

A complete demonstration of the nature of the infecting organism was not essayed. Blood-cultures, however, were made in eleven cases. Only one of them (Case 11) showed the pneumococcus, the others being negative. In Case 6, pneumococci were cultivated from pus from the pleural cavity. Cultures were made from the sputum in several instances.[1] The diagnosis was based on the clinical evidences of pneumonia, special weight being given to the presence of rusty sputum and

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* From the New York Hospital and Research Laboratory, Department of Health, City of New York.

[1] See Notes on Serum, Cultures, Etc., following.

the physical signs of a definite consolidation of the lung. In every case the subsequent course of the illness confirmed the diagnosis of lobar pneumonia and strengthened the probability of the existence of a pneumococcus infection.

The chief points of note in these cases are given in a very condensed form in Table 1, together with the details of the dosage of the serum. The time of onset of pneumonia is not uncommonly indefinite. Many patients give a history of an indefinite illness lasting for several days, during which time they may not have been confined to bed continuously. This may explain the duration of some of the more protracted cases of this series. Most of the patients, however, gave symptoms that fixed the beginning of the pneumonia with a reasonable degree of accuracy.

A review of the data of Table 1 shows that the series included twenty-three cases with sixteen recoveries and seven deaths, a mortality of 30.5 per cent. Of the seven patients who died, three were alcoholics, one of whom had suffered from two previous attacks of pneumonia, and all were very actively delirious. A fourth death was that of a baby (Case 4), who, in addition to pneumonia, had multiple abscesses of the scalp, double purulent otitis media, and empyema followed by pneumothorax. The remaining three deaths seemed to have been due to the frank intensity of the pneumonia.

Of the sixteen patients who recovered, eight had defervescence by crisis and eight by lysis. The crisis occurred on the following days: fourth, fifth to sixth, sixth, seventh, ninth, eleventh, twelfth, and on the eighteenth to nineteenth. The onset of the lysis in the other cases in which the patients recovered occurred on the following days: sixth, seventh (three cases), eighth, tenth and on the thirteenth day. In the remaining cases the onset of the lysis was scarcely definable because the fall of temperature was so gradual. Five patients had complications. In one instance this was serous pleurisy (Case 5). In cases 6 and 19 empyema developed. In Case 4 the signs and symptoms were those of empyema, but an exploratory puncture failed to find the pus. On the next day, however, there was evidence of pneumothorax, and on operation considerable pus was found. Two days later the child died with edema of the lungs. She was extremely ill from the time of admission and had in addition to the pleural complications, double otitis media for which the drum membranes were incised, and also many abscesses of the scalp. Otitis was detected in Case 18 also. The series offered an opportunity to observe the effects of the administration of large and frequent doses of horse-serum that had not been refined in any manner and that contained no preservative except a trace of chloroform.[1] Usually no immediate effects could be detected and the injection of the serum was

TABLE 1.—SUMMARY—

Case No.	Sex,* Age in Years, Habits, Etc.	Condition of Patient				Blood-Culture, Etc.
		Day of Admission	Invasion	Temperature Pulse Respiration	Site Lesion	
1	♂ 12	3	Chill	T. 104°-5° P. 132 R. 28	L. L.	Sterile
2	♀ 1¼	15 (?)	Chill	T. 104.8° P. 160 R. 50	R. U. L. U.	....
3	♂ 41 Alcoholic	8	Chill	T. 103° P. 124 R. 48	R. M. R. L.	....
4	♀ 5	6	....	T. 106° P. 140 R. 48	R. U.	....
5	♂ 26	2	Chill	T. 106° P. 116 R. 28	L. L.	Sterile
6	♂ 17	4	Chill	T. 105° P. 128 R. 40	R. L.	Sterile
7	♂ 30	5	Chilly	T. 103.6° P. 108 R. 32	R. U. R. M.	....
8	♂ 30	2	Chill	T. 105° P. 112 R. 24	R. U.	Sterile
9	♀ 29	2	Cough, pain	T. 103° P. 140 R. 40	R. L.	Sterile
10	♂ 46	7	Chill	T. 104.6° P. 108 R. 32	L. L.	Sterile

* In this column ♂ denotes male and ♀ female.

—OF CASES

Serum Administration			Outcome of Disease			
Day of Disease	Dose, Methods	Effect	Termination of Case	Serum Sickness and Day of Disease it Appeared	Complications	Remarks
4	50 c.c. intrav.	Chill. T. 3°+	Crisis 4th day. Recovery.	Purpuric rash, arthritis 8th day.	....	Crisis a few hours after serum.
15 16 17	30 subc. 30 subc. 30 subc.	....	Crisis 18th and 19th days. Recovery.	....	....	First and second injections without effect.
8 9 10 11	100 intrav. 100 intrav. 100 intrav. 100 intrav.	T. 2°+	Resolution. Death 19th day. Temp. rose 4°: edema of linings.	....	....	Patient alcoholic; acute delirium: edema of lungs. Serum without effect.
6 7 9 11 14	30 subc. 50 subc. 45 subc. 50 subc. 50 subc.	T. 2°— T. 3°—	Death.	Erythema 19th day	Abscess of scalp, otitis media twenty-first day, pyopneumothorax, 600 c.c pus. Edema of lungs, twenty-fourth day.	Serum without any definite effect. Patient very ill on admission.
3 4 5 5 6 7	100 intrav. 100 intrav. 100 intrav. 100 intrav. 150 intrav. 200 intrav.	....	Recovery.	Urticaria fever 17th day.	Pleurisy with effusion 150 c.c. aspirated	No definite effect of serum. Temperature fell by lysis after last injection.
4 7 8 10	100 intrav. 150 intrav. 200 intrav. 200 intrav.	T. 2°—	Recovery	....	Empyema. (Pneumococcus) operation.	Temperature fell gradually after first injection. No effect from later injections.
6	200 intrav.	T. 3°+ T. 3.5°—	Recovery.	Erythema 16th day.	....	Sharp drop in T., P. and R. immediately after serum.
3	80 intrav.	Edema of lungs in one-half hour.	Crisis 9th day. Recovery.	26th day. T. 104°: 27th arthritis.	....	Patient had symptoms of anaphylaxis. Serum stopped; no effect.
4 6	150 intrav. 175 intrav.	....	Recovery.	....	....	Resolution fourth week; no effect from serum.
9	200 intrav.	....	Recovery.	....	....	Temperature fell by quick lysis after serum.

TABLE 1.—

Case No.	Sex,* Age in Years, Habits, Etc.	Condition of Patient				Blood-Culture, Etc.
		Day of Admission	Invasion	Temperature Pulse Respiration	Site Lesion	
11	♂ 39 Alcoholic	6	....	T. 104° P. 100 R. 36	L. U. L. L.	Pneumococcus
12	♂ 16 In extremis	2	....	T. 107°	R. L.	....
13	♀ 2	5	....	T. 105° P. 136 R. 40	L. L.	....
14	♂ 38 Alcoholic; third attack	6	....	T. 103.6° P. 124 R. 24	R. U.	....
15	♂ 24	8 (?)	....	T. 105.4° P. 102 R. 32	R. L.	Sterile Plasmodium malariae
16	♂ 24	3	Chill	T. 105° P. 144 R. 40	L. L.	Sterile
17	♂ 4½	11	Chill, cough	T. 101° P. 118 R. 32	L. L.	....
18	♂ 30 Alcoholic	6	....	T. 105° P. 128 R. 44	L. U.	....
19	♂ 32	4	Chill	T. 104.6° P. 120 R. 44	L. L.	....
20	♂ 13	3	Chill	T. 102° P. 120 R. 48	R. L.	Sterile
21	♂ 54	6	Chill	T. 104.8° P. 88 R. 24	R. U. R. L.	Sterile
22	♂ 20	5	Chill	T. 105.6° P. 120 R. 44	L. L.	....
23	♂ 33 Alcoholic	4	....	T. 102.4° P. 100 R. 48	R. L.	....

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Serum Administration			Outcome of Disease			
Day of Disease	Dose, Methods	Effect	Termination of Case	Serum Sickness and Day of Disease it Appeared	Complications	Remarks
6	200 intrav.	....	Death.	....	....	No effect of serum on T., P. and R. Died three days later.
3	150 intrav.	....	Death.	....	....	Died in eighteen hours.
8	100 intrav.	....	Crisis 12th day. Recovery.	Erythema 14th day.	....	No effect from serum. Crisis fourth day after serum.
6	150 intrav.	T. 2°—	Death.	....	Edema of lungs	Temperature rose steadily; died eleventh day.
9 11	250 intrav. 50 subc.	T. 4½°—	Death.	....	....	Temperature fell after first injection, but rose again and rose after second injection.
4 5	250 intrav. 50 subc.	T. 3°—	Death.	....	....	Temperature dropped after first injection and then rose. No effect of serum.
12	50 subc.	T. 2°—	Lysis. Recovery.	....	....	Temperature fell 2° and then to normal after serum.
6 9	250 intrav. 50 subc.	....	Lysis. Recovery.	13th day rash and fever; 16th arthritis.	....	Slow lysis interrupted by serum sickness.
4 7	250 intrav. 50 subc.	....	Lysis. Recovery.	Arthritis; fever 18th day.	Pleurisy with effusion: tenth day, 700 c.c. turbid serum; 12th. 350 c.c.; 25th. pus.	Serum without apparent effect.
4	250 intrav.	General pains.	Crisis 5th to 6th day. Recovery.	Urticaria after two hours.	....	Crisis twenty-four hours after serum.
8	300 intrav.	....	Lysis. Recovery.	....	....	Lysis rapid twenty-four hours after serum.
6	250 intrav.	....	Crisis 6th to 7th day. Recovery.	....	....	Crisis nine hours after serum.
5	200 intrav.	Nausea, vomiting, pulse rapid and sweating.	Crisis 6th day. Recovery.	....	....	Crisis twenty-four hours after serum.

tolerated surprisingly well. In five patients, however, symptoms appeared that should be mentioned more in detail.

Case 1.—A boy aged 12, received 50 c.c. of serum intravenously on the fourth day of his illness. A few minutes later the patient had a chill and his temperature rose from 104 to 107.2 F. This was followed by a startling drop, and within six hours of the injection his temperature was 97.6 F. The fever did not reappear, and convalescence was prompt and complete. I am inclined to regard this crisis as independent of the treatment, but at the time the sequence of events was very impressive.

Case 8.—The patient was a negro, aged 30, a rather heavy drinker and a driver of horses. When 80 c.c. of serum had run into the vein, he suddenly developed severe dyspnea, a very rapid and weak heart-action, profuse sweating and edema of the lungs. The serum was at once stopped. Within a few minutes the symptoms began to abate and within half an hour the lungs were nearly clear and his condition was satisfactory. The subsequent course of the pneumonia was typical and but moderately severe. Six days later, on the ninth day of the disease, defervescence by crisis occurred. Convalescence was interrupted only by symptoms of serum sickness.

Case 20.—A boy aged 13, during the introduction of the serum complained of headache, pain in the abdomen and later in the legs. The pulse was accelerating and the serum was stopped, but not until he had received 200 c.c. Two hours later a profuse urticarial rash appeared on the abdomen and lasted a few hours. The patient had no late symptoms of serum-sickness.

Case 23.—A man, aged 33, a heavy drinker, when 150 c.c. of serum had been given, became nauseated and vomited. These symptoms ceased in about five minutes and 50 c.c. more of serum were given. At this time the pulse became rapid and the patient broke out in a profuse sweat. The serum was stopped and in a few minutes he was comfortable. He likewise had no late serum symptoms.

The effect of the serum on the leukocytes was determined by frequent blood-counts before and after the injections. No constant effects on the white cells could be made out. The results of some of these counts are detailed in Table 2.

Late symptoms due to the serum were noticed in eight patients. In consideration of the large doses of unrefined horse-serum, this is not a surprisingly large number. The symptoms were not usually severe.

During the time of this experiment the First Medical Division of New York Hospital treated fifteen cases of pneumonia with six deaths, a mortality of 40 per cent., as compared with 30.5 per cent. for the serum cases. Of their ten cases with recovery, in six, or 60 per cent., there was defervescence by crisis. In the serum cases 50 per cent. of the patients who recovered had crisis. Only two of the control cases had complications, a percentage of 13.3. In the serum cases five patients, 22 per cent., had complicating inflammations. It does not seem that these were due to the use of the serum, but the number of patients with inflammations of the pleura (four cases, 17.4 per cent.) is uncomfortably large.

TABLE 2.—Blood-Counts Before and After Injection

Case No.	Dose of Serum	Serum, c.c.	Leukocyte Counts					
			Before Serum		After Serum			
			No. of Cells	Percentage of Polynuclears	Hours After Serum	No. of Cells	Percentage of Polynuclears	Note
1	first	60*	25,000	86.5	2	19,000	85	
					4	30,000	87	Crisis
					6	29,000	81	
					18	20,000	69.5	
					27	14,000	44.7	
2	first	30†	15,000	81.0	3	14,500	65	
					5	12,700	70	
					14	10,500	76	
	third	30†	13,000	70.0	2	12,900	70	
					13	11,000	70	
					36	15,900	71	
3	first	100*	50,000	94.5	2	49,500	95	
					4	50,000	91	
					16	55,000	97	
5	first	100*	24,400	85.0	2	26,900	92.5	
					4	25,000	86	
					6	25,400	89	
					8	25,900	88	
					10	24,500	88	
					21	20,000	85	
6	first	100*	27,800	88.5	2	29,000	91.5	
					4	26,900	94	
					6	28,800	93	
10	first	200*	20,800	93.5	2	29,000	94	
					4	27,000	93	
					6	23,000	90	
					18	21,100		
16	first	250*	14,000	86.0	2	16,400	92	
					4	15,400	89	
					6	12,200	84	

* Intravenous injection. † Subcutaneous injection.

A study of the results of this treatment leaves one doubtful of the influence of the serum, in modifying favorably the course of the pneumonia.

The prosecution of this experimental study necessitated much extra work in the wards and laboratory. This was performed by the members of my house staff, Drs. Howard, Kutil, Alling and Wildman. I wish to thank them for their enthusiastic willingness, which made these observations possible.

NOTES ON SERUM, CULTURES, ETC.

CHARLES KRUMWIEDE, JR., M.D., NEW YORK

The serum was prepared by injecting a horse with pneumococci from varied sources. These cultures were all typical inulin fermenting types. They were isolated from the mouth in cases of Riggs' disease, from the sputum in cases of lobar pneumonia, from empyema, and from the meninges and blood of septic infections following the exanthems. The cultures used varied from time to time. As fresh cultures were isolated the older cultures were dropped. No attempt was made to raise the virulence of these cultures by passage through rabbits or mice. Although this may influence the protective value of the serum for these animals, it is open to question what influence such adaptation to a new host has on the curative value in man. The cultivation on artificial medium undoubtedly changes the pneumococci, but how far this influences their ability to stimulate curative substances in the horse is unknown. The purpose was to prepare an immune serum against the prevailing strains of pneumococci, using the strains as little removed from human sources as possible; and to test the value of such serum for general use, where the immunological tests on each case would be impossible.

The injections at first were cultures in broth to which was added horse-blood. Later the cultures were grown on agar and washed off with water. At first the increasing doses were of cultures which had been heated to 55 C. for one hour. When the dose had reached the maximum decided on, live cultures alternating with autolysate were used. The autolysate was prepared by allowing distilled-water suspensions of the cocci to stand in the ice-chest for one week. The live cultures or the autolysate were added to the heated vaccine, in increasing amounts, until only the unheated culture or autolysate was given.

The injections were given once a week subcutaneously. The maximum dose equaled the growth on agar in 10-pint Blake bottles. The horse was receiving the total amount of live and autolyzed cocci at the time it was supplied to Dr. Williams. The bleedings were made every two weeks. Every effort was made to supply the fresh serum to avoid any possibility of deterioration. After the serum was drawn from the clot, several cubic centimeters of chloroform were added to each liter. In bottling the serum for use, the supernatant serum was drawn off and the lower portion containing sediment and excess of chloroform discarded.

The material from the cases was examined both for diagnosis, and in the hope that the cultures isolated could be studied for their complement-fixing power, with the serum used, and that the protection value of the serum could be tested on the type of pneumococci found. This study was not made, partly because of other work, and partly because the strains were found to possess such low virulence for rabbits. When the intravenous inoculation of the growth from one blood agar slant was given, only two strains killed, one in forty-eight hours, the other after ten days. Cultures isolated from the heart's blood of these rabbits did not kill other rabbits when a somewhat smaller dose was used. The sputum from Cases 18 to 23, inclusive, was examined. They all showed an overwhelming preponderance of typical pneumococci. One case of the series showed the presence of an abundance of *Streptococcus mucosus*.

BOOK REVIEWS

MATERIA MEDICA, PHARMACOLOGY, THERAPEUTICS AND PRESCRIPTION WRITING FOR STUDENTS AND PRACTITIONERS. By Walter A. Bastedo, Ph.G., M.D., Associate in Pharmacology and Therapeutics at Columbia University. Cloth. Pp. 602. Illustrated. Philadelphia and London: W. B. Saunders Co., 1913.

The author believes that we are at the dawn of a new era of simple and practical therapeutics as the outcome of the adoption of laboratory methods in clinical research. For this reason he has given special prominence to the discussion of clinical studies on the action of drugs. It is this which gives the book its most striking character, namely, that it is right up to date. To the busy practitioner who has not had the time to keep up with the reading of the vast bulk of current literature this book ought to be most welcome. To the student this book offers, in a compact and most readable manner, a good practical course in these subjects; perhaps more practical and more useful than most of the other books on pharmacology and therapeutics at present in use.

It is perhaps somewhat unfortunate that the author has seen fit to use a therapeutic classification, for though it might be admitted that any classification in pharmacology is more or less unsatisfactory the therapeutic classification is the least systematic: for use that is made of drugs is after all more or less accidental rather than intrinsic. A certain amount of "lack-of-balance" in the treatment of the various topics becomes apparent, as, for instance, the large amount of space given to digitalis and the somewhat scanty discussion of some of the heavy metals. Under the heading of Cathartics a very brief discussion of the causes of constipation is introduced, which is probably not only unnecessary but even undesirable in a book of this character. Nevertheless Bastedo has given us a valuable text-book which it seems is destined to make a place of its own in this field.

PROTEIN SPLIT PRODUCTS IN RELATION TO IMMUNITY AND DISEASE. By Victor C. Vaughan, Victor C. Vaughan, Jr., and J. Walter Vaughan. Cloth; price, $3.00, one volume; total pp. 474. Philadelphia: Lea & Febiger, 1913.

The book describes the work of fifteen years along a well defined line of thought. Those who have followed the publications from Vaughan's laboratory during these years know what opposition many of his beliefs have encountered, so that it is with real enthusiasm that one reads the clear, simple statement here presented. For it is obvious that almost all his tenets have been amply upheld by recent workers in immunity.

The preface contains a general consideration of the chemical forces that work in the living cell, and the introduction deals with the subject of the protein structure of bacterial cells. It is pointed out that like all other proteins, bacterial proteins can be split by chemical agents or ferments into a very poisonous portion and a non-toxic residue. The remnant of the book is concerned with a discussion of these split products and their relation to sensitization, immunity and disease. The work advances in a most orderly and logical fashion. The toxic portion is first established as a true protein by an exhaustive series of chemical analyses, and then there follows a description of its preparation and physiological action. It is clear from these physiological tests that what Vaughan and his co-workers saw many years ago in the behavior of animals injected with his "poisonous portion" was the now well-known phenomenon of anaphylaxis. The identity of the author's "poisonous portion" and Friedberger's anaphylatoxin is discussed at great length and with many varying points of view throughout much of the rest of the book. The two substances seem to be identical.

Chapters 8, 9 and 10 deal respectively with tubercle bacillus protein, anthrax and pneumococci. Two important points are made in these chapters. It is shown that the poisonous group (toxophor) of the tubercle bacillus kills, as all other toxic groups do, with the symptoms of anaphylaxis, but has no sensitizing power. The non-toxic cell residue, however, can sensitize guinea-pigs to living tubercle bacilli. In experiments with anthrax and pneumococcus proof is advanced to support the hypothesis that pathogenicity does not depend on the amount of the toxic substance, but on the ability of micro-organisms to live and multiply in the body; that is to convert human proteins into bacterial proteins.

In Chapter 11, which occupies about one-quarter of the book, the whole subject of anaphylaxis and protein sensitization is discussed. The argument, following a short historical sketch of the knowledge of anaphylaxis, is in presentation of the author's theory of the mechanism of anaphylaxis. Contrary to the generally accepted view that a mixed protein like blood-serum contains one protein which sensitizes and another which is toxic, he believes that the sensitizing and toxic proteins are groups in the same molecule. The process of sensitization confers the power on certain body cells of splitting such a protein molecule and liberating the toxic portion.

The chapter on protein fevers is most interesting and the protocols and charts quite conclusive. The last chapter, dealing with the phenomenon of infection, is likewise most suggestive and instructive. Here, as elsewhere in the book, it is strongly urged that vaccine therapy has great dangers as well as power to help. Consequently the author seeks the soluble protein sensitizer free from its toxic group. The book is so full of ideas and of sound experimental observation that a full discussion would require much more space. It is an exceptionally good piece of work, suggestive and stimulating, and the record of a most thoughtful and purposeful effort to demonstrate the obscure relationships of the protein poisons and infectious diseases.

A CORRECTION

New York, May 25, 1914.

To the Editor, Archives of Internal Medicine:—In the article printed in your valuable journal for March, 1914, on Ulcus Ventriculi, by myself and Dr. I. W. Held, I find the quotation from the article of J. Kauffman entitled, "Mangel an Magen-Schleim," from the *Archiv für Verdauungs-Krankheiten*, 1907, p. 616, to be incorrect. The first sentence reads that in hyperacidity the mucus in the stomach is increased. J. Kauffman found that in cases in which there is a diminution in the normal mucus of the stomach there is pain simulating hyperacidity, although the acidity is normal. On that he bases his assertion that silver nitrate is beneficial in cases of irritation of the stomach in which the mucus is diminished.

M. H. Gross.

40 East Forty-First Street.

A CORRECTION

Dr. Edward Perkins Carter wishes to make correction in the figures as they appeared in the manuscript of his paper on "Clinical Observations on Defective Conduction in the Branches of the Auriculoventricular Bundle," in the May, 1914, number of the Archives, at page 801, as follows: Page 809, line 26, for "0.13 and 0.18" read 0.12 and 0.20; p. 809, line 27, for "0.18" read 0.20.

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